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THE MILITARY ENVIRONMENT PRIMARILY IN RELATION TO CHANGES IN BAROMETRIC PRESSURE AS APPLIED TO CLINICAL MEDICINE

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LECTURE I: THE EFFECTS OF COMPRESSION

The art and science of civilian medical practice in relation to the care of sick or injured patients usually require but little modification for application in military service. Not only are reserve medical officers capable of fulfilling the professional duties of the military hospital, but the tremendous stimulus that warfare provides for new or improved therapeutic measures is reflected by the many developments that originate and are fostered in the reservoir of civilian experience. The preparation of plasma, for example, by John Elliott of Salisbury, North Carolina, and its utilization by physicians in this state preceded and later facilitated the efforts of Commander Lloyd Newhouser and Major Kendricks to accomplish one of the truly life saving achievements of the present war.

The civilian physician, moreover, is becoming increasingly familiar with those conditions affecting large groups of people in industry that produce overcrowding, fatigue, and accidents inherent in the operation of stationary and mobile machinery. The preventive measures applied are again common to both civilian and military life.

It is that phase of military life, however, dealing with the effect on healthy men of such deleterious but not immediately incapacitating environmental factors as noise and vibration, unaccustomed motion, and accleration, periods of monotony and confinement punctuated by the performance of gruelling tasks, extremes of temperature, and wide variations of barometric pressure that may be unfamiliar to the physician in civil life.

To evaluate the harmful effect that these influences exert, and to provide protective measures that prolong the fighting life of the individual are tasks that often require long and intimate experience with military operations. Since these harmful forces tend to create a condition of irreversible functional breakdown, the military surgeon strives not only to exercise protective measures, but also to train and condition the individual so that the requisite adaptation to the adverse environment will be facilitated.

It is the purpose of these lectures to describe phenomena observed in the military environment that may be of particular interest in view of their relationship to certain aspects of clinical practice. Of these phenomena alterations of barometric pressure affecting divers and aviators produce tangible derangements that are not wholly divorced from clinical civilian experience.

The Nathalie Gray Bernard Lectures. Presented at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem.

(The contents of this paper are not to be interpreted as an official expression of the Navy Department.)

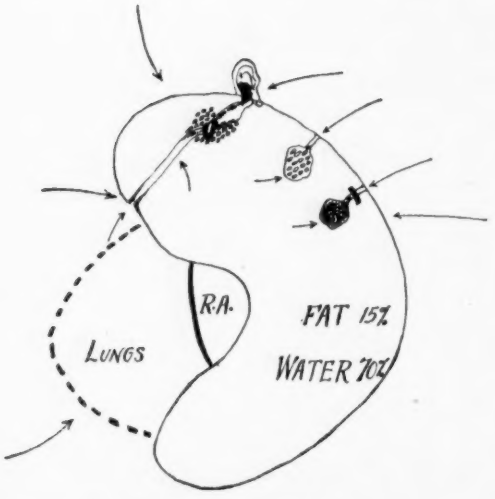

Fig. 1. This diagram illustrates the effects of pressure on the body, showing equalized pressure on the tympanic membrane and in a sinus space, and congestion and hemorrhage into a sinus space when the opening into the sinus is blocked, preventing equalization of pressure. From Behnke, A. R.: High Atmospheric Pressure, Ann. Int. Med. 13:2217-2228 (June) 1940.

The Effect of Compression

In a study of the effect of pressure one may consider that the native pearl diver is subjected to an additional compressive force of one atmosphere for every 33 feet of descent in sea water. At a depth of 100 feet, for example, the total pressure acting on his body is approximately four atmospheres.

At this depth the air in the diver's chest is compressed to one-fourth of the initial volume, since the pressure within the lungs is increased fourfold (fig. 1). The depth, therefore, to which the unprotected diver can descend appears to be limited by the ratio of chest volume to residual air volume. The force of compression acts also to move air into the spaces of the middle ear and sinuses, so that the pressure within them is made equal to that outside.

The phenomenon of interest in connection with compression is the absence of symptoms, provided that the pressure is equally distributed on all parts of the body. Apart from the hydrostatic compression of the thorax and abdominal viscera containing gas, demonstrable change is not observed.

If the diver is compressed in a naval recompression chamber there is even less alteration, since the thoracic volume is unchanged (fig. 2). At a pressure of sixteen atmospheres, equivalent to a depth of 500 feet, one observes no symptoms arising from compression of protoplasm, provided that air has free access to all surfaces of the body, such as the membranous linings of the frontal sinuses, the ethmoid and the mastoid air cells.

On the other hand, an unequal distribution of pressure—that is, a difference in pressure of 1/16 of an atmosphere or less than 50 mm. of mercury or 1 pound per square inch —acting on the body induces the symptoms of pain and the concomitant pathologic alterations of congestion, edema, and hemorrhage (fig. 1).

Referring again to the native diver submerged at a depth of 100 feet, we observe that the initial chest volume of 6,000 cc. has been reduced to 1,500 cc. If the diver descends to greater depths the additional hydrostatic pressure, unable to compress further the rib cage, will bring about a condition known as a "squeeze".

The effect of the "squeeze" is to force

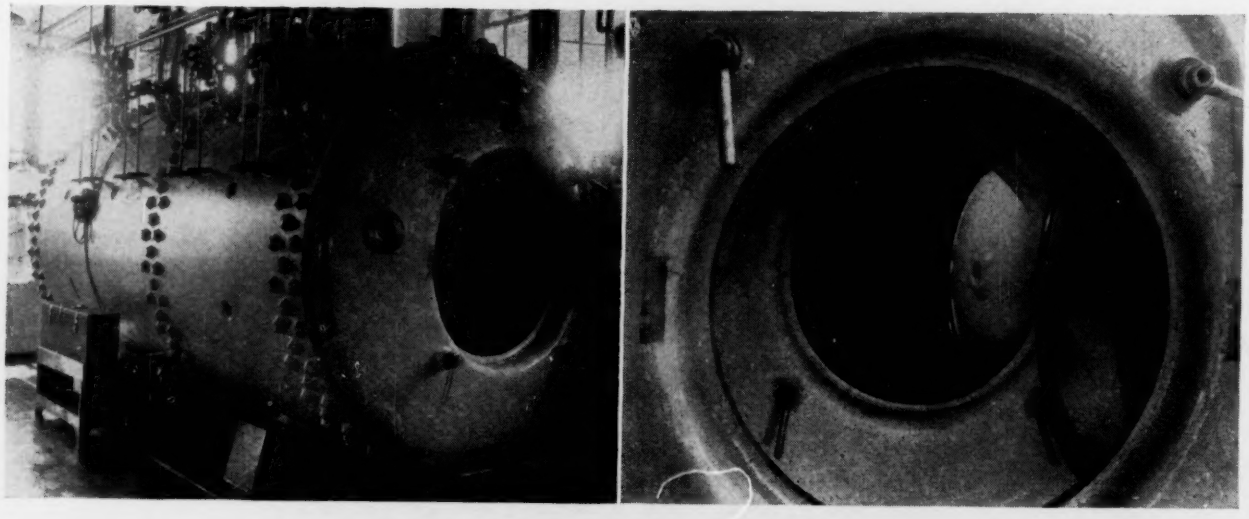

Fig. 2. Photographs of a Naval recompression chamber.

blood and tissue fluid into the relatively decreased pressure area created in the residual pulmonary air. Thus we see that nature not only abhors a vacuum, but also is not on friendly terms with a difference in pressure. Equalization of pressure tends to be restored by the accumulating transudate, but it is at the expense of the tissue.

In a similar manner aural and sinal membranes are injured by a "squeeze" if the corresponding channel openings do not permit the free ingress of air.

During the past twelve years thousands of our submarine personnel have been subjected to 50 pounds per square inch excess pressure in the naval recompression chamber in connection with the submarine escape drill. From 5 to 25 per cent of the trainees at any given time have been unable to accommodate readily the excess pressure by reason of "colds" or varying degrees of infection of the upper part of the respiratory tract which act to seal the openings of the auditory tubes, and less frequently the sinal meatuses.

In aviation during descent from high altitudes the increased pressure similarly affects individuals to create a condition termed aerootitis media by Armstrong and Heim. In civilian aviation the stipulation that passenger aircraft must descend at a rate not greater than 300 feet per minute was based upon the difficulty generally experienced in accommodating the increased pressure.

In the pressure chamber the familiar anatomic alterations are conveniently studied by observing the tympanic membrane. As the pressure is increased, the tympanic membrane on the side of the blocked auditory tube is pushed inward, blood vessels appear over the handle of the malleus as a fine radiating network, the membrane loses its luster and then becomes suffused with blood. Differences in pressure of about 50 mm. of mercury suffice to bring about these changes. Presumably these derangements affect the lining membrane of the whole middle ear space and mastoid air cells.

Similar changes are known to take place in the sinuses, since frank hemorrhage has been induced by the differential pressure.

A poorly filled tooth containing an enclosed pocket of air will likewise be injured by the difference in pressure.

Pain is the concomitant symptom elicited by the unequalized pressure, and is confined to the area affected. With reference to the ear the pain may be felt over the mastoid area as well as in the auditory canal. The particular obstructed sinal space and even the defective tooth make their presence known by the specific and sharply circumscribed pain.

Illustrative of the same type of trauma is the otitis media following high altitude flight, and indirectly brought about by oxygen inhalation. Air leaves the aural spaces during ascent to high altitudes and is replaced by oxygen during descent. When the ground level is reached the aviator may be entirely free from symptoms during the daytime. During sleep, however, oxygen continues to be absorbed, and the suspension of the voluntary effort to swallow results in a cupping action on the middle ear tissues.

The symptoms and signs of the oxygen otitis media are indistinguishable from those arising from obvious pressure trauma. This troublesome condition can be relieved when air is substituted for oxygen inhalation during descent from the 12,000 foot level.

Effect on Hearing:

Although the pathologic disturbances may be severe, our observations point to the conclusion that even such extensive effects of pressure trauma as hemorrhage and perforation of the membrane are quickly repaired. Acuity of hearing is temporarily decreased throughout the whole range of the audiogram, but in contrast to the effect of gunfire, evidence at hand does not indicate that there is permanent deafness.

Complications of suppurative otitis media and pansinusitis are infrequent if the individuals affected stay out of the water. The spread of infection by air forced into the enclosed spaces does not appear to be an important factor in this condition.

In clinical practice a form of catarrhal otitis media and the frontal "vacuum" headache simulate closely the type of trauma ascribed to negative pressure.

The occlusion of an auditory tube or frontal sinus leads to a partial absorption of oxygen proportional to the difference between the pressure in the air of 159 mm. of mercury and the pressure in the lining membrane of less than 40 mm. of mercury. Such disturbance gives rise to the type of pain and the pathologic picture described for the

acute injury observed in the pressure chamber.

It is recognized that in children and infants the presence of adenoid tissues around the opening of the auditory tube may render more frequent the occurrence of catarrhal otitis media during inflammation of the nasopharynx. That the concomitant pain may be referred to the mastoid area, which is tender to palpation, indicates not necessarily an infective process, but a pressure trauma brought about by the rather complete absorption of the incarcerated oxygen.

The Pressure Chamber as a Diagnostic and Therapeutic Appliance

Consideration may, therefore, be given to the utilization in civilian life of small pressure chambers by both otolaryngologist and bronchoscopist for diagnostic and therapeutic purposes. We have come to regard the pressure chamber as a valuable diagnostic device that enables us to ascertain quickly the patency of the auditory tube and the sinal meatus. In a measure it serves also as a presumptive test for physical fitness. Those individuals who are able to tolerate increased pressure at a rate of about 30 pounds per square inch per minute are generally free from infection of the upper part of the respiratory tract. In this day of prevalent acute or subclinical nasopharyngeal infection, pressure tolerant individuals form the more rugged body of our population.

As an appliance for bringing about ventilation and drainage of aural sinal spaces, the chamber has proved to be effective whenever we have had occasion to treat our divers. In contrast to some types of suction apparatus, the chamber procedure is physiologically sound.

Disturbances of Gaseous Equilibriums

The profound physiologic responses incident to an alteration in pressure are related to disturbances in gaseous equilibriums. On compression, the nitrogen in the air will be absorbed by the circulating blood and transported to the body solvents, fats, and fluids.

The manner of absorption of atmospheric nitrogen is shown by figure 3. Actually curve "A" is based upon measurements of the dissolved nitrogen removed from the body of an individual during a six hour period of oxygen inhalation. The hypothetical curves "B" and "C" represent the absorption or

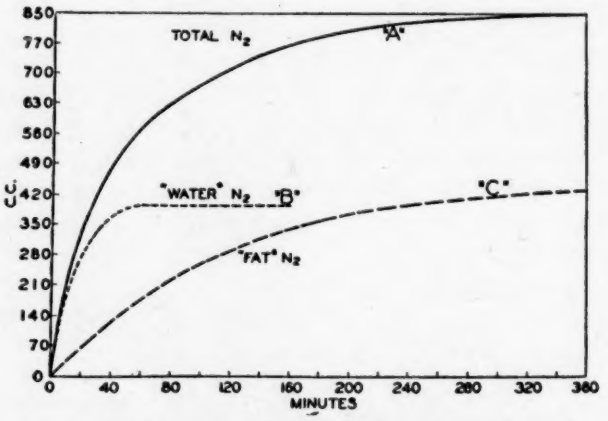

Fig. 3. Total N_2. (A) represents the average of the values for nitrogen elimination from three men (average weight 64 Kg.) who breathed pure oxygen at atmospheric pressure. "Water" N_2 (B) and "Fat" N_2 (C) are hypothetical curves showing the absorption and elimination of nitrogen by the body solvents. The values for nitrogen on A are approximately the sum of corresponding values on B and C.

From Behnke, A. R.: Application of Measurements of Nitrogen Elimination to the Problem of Decompressing Divers, U. S. Nav. M. Bull. 35:219-240 (April) 1937.

elimination of nitrogen from body fluids and fat respectively.

The nitrogen curve represents essentially the absorption and elimination of all inert gases. Ether vapor, for example, is absorbed by the body in a similar manner. Departure from the nitrogen curve will depend upon the distribution coefficient of the gas between the air in the lungs and the blood.

It would be expected that a given pressure of cyclopropane in the lungs would require many hours to come into equilibrium with the pressure in the body, in view of its high fat-water solubility ratio (35 to 1) in contrast with ether or nitrogen, which possesses a corresponding ratio of 5 to 1. Fat, therefore, acts as a gaseous reservoir.

The ether absorption curve, on the other hand, is expected to differ from the nitrogen curve by reason of the high solubility of ether in blood and the consequent delay in attainment of equilibrium between the ether pressure in the lungs and the blood. The absorption of carbon monoxide by the blood illustrates the importance of the distribution coefficient in the attainment of equilibrium between the gas in the alveoli and the blood when the disparity in the distribution ratio is great. By contrast, the low solubility of nitrogen in blood permits the immediate attainment of equilibrium between the alveolar gas and the blood.

Quantity of Gas Dissolved in the Body:

From the composition of the body in terms of fluid and fat the quantity of gas absorbed can be computed on the basis of the solubility coefficient. At normal barometric pressure 800 to 1200 cc. of nitrogen are absorbed by the tissues of the body and divided about equally between the fluids and fat.

In regard to ether, the pulmonary concentration required to maintain anesthesia, 3 per cent, will under conditions of equilibrium be associated with an intake of about 40 liters of the vapor, equivalent to about 170 cc. of liquid ether.

Narcotic Action of Nitrogen:

When the air pressure is raised about four atmospheres—equivalent to a diving depth of 100 feet—the atmospheric nitrogen, wholly benign at normal pressure, acts as a narcotic substance to impair neuromuscular coordination and to slow cerebration.

One of our student divers, when asked how he felt on his first deep dive, replied, "I felt as though I were drunk on the bottom"; but he concluded, "It was the best dive yet."

The nitrogen intoxication is in fact closely allied to alcoholic manifestations, to the effects of anoxia, and to the responses associated with that large group of substances that depress the function of the nervous system. The pleasant initial state of euphoria later exacts its toll of irritability, drowsiness, and the need for sleep.

During salvage operations undertaken to raise the U.S.S. SQUALUS, one of the divers at a depth of 220 feet forgot his task and called out a series of football signals from the deck of the sunken submarine. The futility of employing air as a breathing medium was demonstrated by another abnormal response. A diver, in the belief that he was about to remove an obstruction, attempted to usurp the task of the Fate Atropos in his effort to sever his own air and lifeline. The following statement of one of the divers illustrates the helplessness that may attend the inhalation of compressed air:

"I made a normal descent, but as I started to get aboard the submarine I had a turn around my leg with the descending line. Had to struggle a bit to get it clear. Got on the submarine, called "topside" and reported. Did not hear any answer. I am not sure, but I think that I asked them if they heard me, to give me the telephone signal on my life line. I must have lost consciousness, for the next thing I remember is that I was jerked up off the submarine. I must have had control of myself on the way up, for when I regained consciousness I had the control valve in my hand."

That the presence of carbon dioxide in the diver's helmet augmented the symptoms cannot be doubted from the subsequent experience with the synergistic action of this gas. Carbon dioxide, by virtue of its augmentative effect on cerebral circulation, tends to render more effective a given gas pressure in the lungs. The impairment in function during the inhalation of air in the pressure chamber at a simulated depth of 300 feet was in no way comparable to the helplessness of the divers working at a depth of 240 feet.

The successful outcome of the submarine salvage operations was due to the employment of helium as a substitute for the nitrogen of the air. Thus, the inhalation of mixtures of helium and oxygen has provided atmospheres conducive to efficient activity at depths up to 500 feet, or under conditions in which the inhalation of air would have terminated in unconsciousness.

As to the cause of the non-activity of helium in contrast with nitrogen, one may consider that a physical property is operative, since argon, although possessing chemical inertness as does helium, nonetheless elicits the nitrogen type of narcosis. Of the physical properties the oil-water solubility ratio and the molecular weight may be important. In accord with the Meyer-Overton concept is the fact that helium possesses an oil-water solubility ratio one-third that of either nitrogen or argon.

Whatever the physiologic basis of action, the intriguing fact is that atmospheric nitrogen, an elementary and benign gas as it exists in the body at normal pressure, will induce a narcotic type of unconsciousness at high pressure.

Effect of Oxygen at High Pressures:

The period of time that pure oxygen can be safely breathed at sea level pressure has not been determined. The dog, rabbit, rat, and other small animals develop pulmonary edema and hemorrhagic extravasation after twenty-four to forty-eight hours' exposure in the concentrated oxygen atmosphere. In

man, contradictory reports of oxygen tolerance arise, perhaps from the failure to consider that healthy men may react differently from patients, and that interruption of oxygen inhalation for short periods of time or a decrease in the percentage breathed fortifies resistance to toxic symptoms. It should be emphasized that the administration of oxygen as clinically employed is usually well within the limits of tolerance. Under certain conditions, however, healthy men complain of irritability and irritation of the nasopharynx following prolonged (six to seventeen hours) inhalation *without interruption* of 99 per cent oxygen.

If in a pressure chamber an individual breathes oxygen instead of air a series of wholly different phenomena supervene.

At a pressure of three atmospheres the oxygen absorbed in the lungs and transported in physical solution in blood is adequate to meet tissue requirements so that the oxyhemoglobin is not reduced in its passage through capillaries. This seemingly desirable condition of complete redbloodedness is marred usually during the fourth hour of oxygen inhalation by a progressive contraction of the visual fields which terminates in amblyopia (fig. 4).

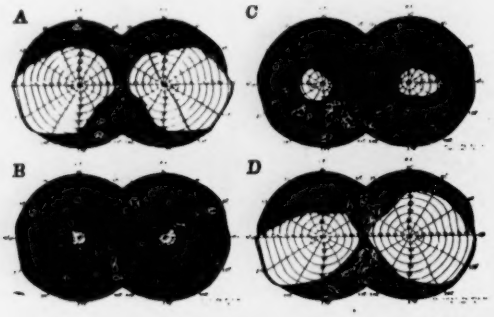

Fig. 4. Perimetric measurements made before and after three and one-half hours' oxygen breathing at three atmospheres' pressure (30-lb. gauge). A represents normal field limits, the determinations being made with the Ferree-Rand perimeter and exposure method with 7 foot-candles illumination. B, C, and D represent field limits 5, 25, and 50 minutes, respectively, following three and one-half hours' oxygen breathing, observations being made at atmospheric pressure with a black perimeter of 25 cm. radius illuminated by a blue bulb placed behind and above the observer's head; moving stick stimuli were used and checked by the exposure method; the test object was a white disc 6 mm. in diameter.

From Behnke, Forbes, and Motley: Circulatory and Visual Effects of Oxygen at Three Atmospheres Pressure, Am. J. Physiol. 114:436-442 (Jan.) 1936.

Characteristic of the action of oxygen is the disappearance of these alarming symptoms when air is again breathed.

If now the ambient pressure is raised to four atmospheres or higher, oxygen inhalation is accompanied by convulsive seizures and at times an aura. Except for an increased intensity, this condition simulates the convulsive states of idiopathic epilepsy. Recovery, again apparently complete, attends the substitution of air for oxygen.

Perhaps no other agent is capable of bringing about similar responses that exhibit the reversibility characteristic of oxygen poisoning.

Mention may be made again of the influence of carbon dioxide, which renders a given oxygen pressure in the lungs more effective by bringing on the earlier onset of symptoms or their appearance at a lower pressure level.

Pressure thus serves to alter the properties not only of innocuous nitrogen but also of life sustaining oxygen. When the door of the pressure chamber closes, one gas may become a narcotic substance, the other a convulsive agent.

Lecture II

The Effects of Decompression

Overdistention of the Lungs

Following submarine disasters in 1925 and 1927 the Navy Department developed two types of appliances to enable personnel to escape from sunken craft. In the steel bell, devised for collective rescue, there are no physiologic or clinical considerations involved unless we consider the problem of claustrophobia.

The second appliance, essentially a rebreathing bag, was associated with a number of accidents in the early days of submarine escape training (fig. 5). In operation the "lung" device is inflated with oxygen at a pressure equal to the water pressure at the depth of submergence. When the submerged individual ascends to the surface, the compressed gas in the lungs and in the breathing bag must escape through a relief flutter valve located on the bottom of the appliance if the intrapulmonic pressure is to be maintained at a level equal to the hydrostatic pressure.

Although the majority of trainees made normal practice ascents, it was observed

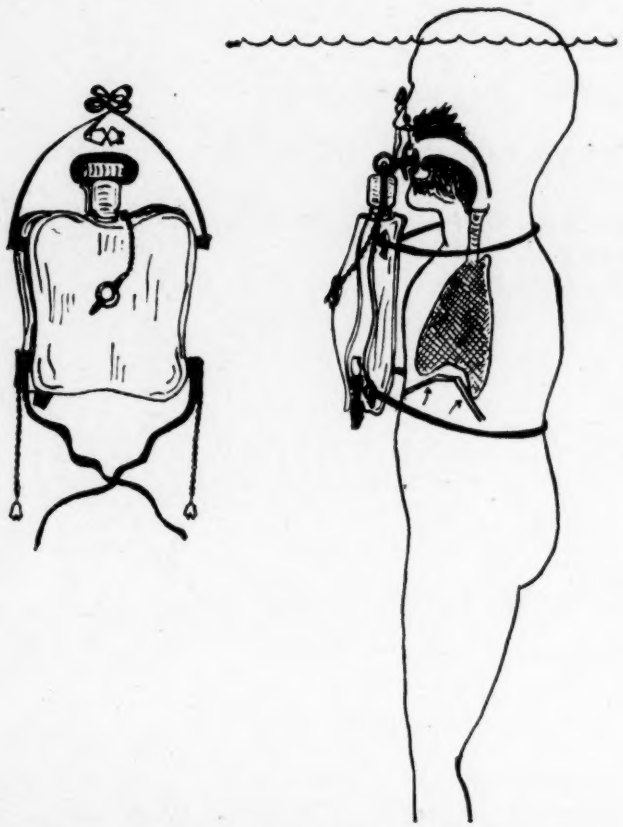

Fig. 5. Submarine escape appliance is a rebreathing device with a relief flutter valve located at the bottom of the reservoir bag fifteen inches below the mouthpice. During ascent the lungs tend to be distended by a pressure equivalent to the weight of the fifteen inch water column.

that occasionally an individual after reaching the surface of the water would lapse into unconsciousness. The following description is typical:

"About a minute later he slowly collapsed in the water. . . . The extremities and body were cold and the muscles were rigid. Breathing was shallow and rapid and the pupils were dilated, but reacted to light. The radial pulse was absent and the heart seemed slow and weakened. After about 15 minutes the patient began to make groaning sounds and to roll his eyes about. . . . He was then dressed, but gave no assistance to this act and made thrashing, and apparently hysterical movements with the arms and legs. . . . When seen about a half hour later he complained of loss of vision, even to light, and anesthesia of the left foot and leg."

The cause of these accidents, at first obscure, was clarified by the realization that a frightened man might hold his breath and that spasm of the glottis sealing the trachea would permit the expanding gas to overdistend the lungs, rupture the alveoli, and force gas in the free state into the pulmonary circulation. Subsequently these gas bubbles formed emboli which gave rise to asphyxia, paresthesias, paralysis, and loss of consciousness.

In corroborative experiments on the anesthetized dog an intrapulmonic pressure in excess of 80 mm. of mercury applied for periods of ten seconds or longer was associated with the presence of free gas in blood vessels.

Accidents connected with practice escapes have occurred at depths of only 15 feet. On the other hand, the native diver may ascend to the surface without injury from depths of 100 feet. In the case of the trainee the compressed air at a depth of fifteen feet may not be able to expand without rupturing alveoli in a rapid ascent to the surface. The lungs of the native diver, however, in his rapid ascent to the surface cannot be expanded beyond the volume present on the surface at the beginning of the dive.

When the etiology of the submarine escape accidents had been ascertained, it followed that prevention of pulmonary overdistention was a matter of proper ventilation of the lungs and that the appropriate treatment of injured men was compression in a chamber. This procedure has been successfully applied in the treatment of extensive traumatic gas embolism.

In subsequent practice ascents it has been possible to fill the lungs with compressed air at a depth of 100 feet and then ascend rapidly to the surface. If one holds his breath at the beginning of the ascent, a sensation of substernal distress, and a feeling of actual stretching of the lungs soon forces an exhalation.

Accompanied by continuous exhalation an ascent from a depth of 100 feet can be made during a period of twenty seconds without danger, although a similar ascent might be fatal from a depth of only 15 feet if the breath were held.

At present thousands of submarine personnel are trained without a single mishap. Every submarine that leaves port is now manned by a crew whose morale has been strengthened by training in the method of escape from disabled, sunken craft.

Clinically our interest in overdistention of the lungs centers in appliances designed to promote artificial respiration by periodic in-

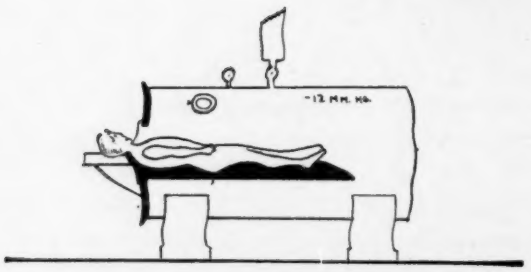

Fig. 6. This diagram illustrates the principle of Drinker and Emerson respirators.
From Behnke, A. R.: Certain Physiological Principles Underlying Resuscitation and Oxygen Therapy, Anesthesiology, 2:245-260 (May) 1941.

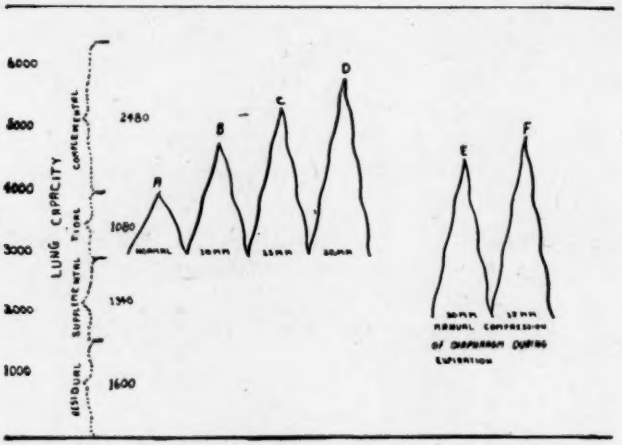

Fig. 7. The average values for the tidal air volume of seven healthy men.
A. The effect of positive pressure inflation for five seconds.
B. 10 mm. mercury pressure.
C. 15 mm. mercury pressure.
D. 20 mm. mercury pressure.
E. 10 mm. with subject on side and manual compression of diaphragm.
F. 15 mm. under same conditions.
From Behnke, A. R.: Certain Physiological Principles Underlying Resuscitation and Oxygen Therapy, Anesthesiology, 2:245-260 (May) 1941.

flation of the lungs. Insofar as expansion of the lungs is concerned there appears to be no difference between the effect of a decrease of pressure around the chest wall, as in the Drinker or Emerson respirator (fig. 6), and inflation of the lungs through a mask or catheter.

An essential consideration is the amount of pressure required for effective ventilation. The factor of pressure is of little significance when it is separated from the time factor. A pressure of 15 mm. mercury, for example, applied in alternate three second cycles will not produce the distention associated with the same pressure applied in six second cycles, although the total gas exchange is the same.

In tests performed on healthy men to determine the effective degree of inflation without overdistention of the lungs, it was found that pressures of 20 to 25 mm. of mercury applied alternately for periods of five seconds to induce respiration caused substernal distress, or the same sensation felt during rapid ascent with the submarine escape appliance. Pressures of 10 to 15 mm. of mercury, however, applied in alternate 5-second periods were well tolerated.

Figure 7 illustrates the tidal air volumes for normal breathing and those following mechanical distention of the lungs. Graphs E and F of figure 7 represent the increased effectiveness of pulmonary ventilation brought about by manual compression of the diaphragm during expiration when the subject was placed on his side. Compression of the diaphragm was not effective with the patient lying on his back.

In regard to the employment of negative pressure the question of injury to the lungs is paramount. Pressures of 9 mm. of mercury or less are well tolerated by healthy men. But the value of such pressure in promoting pulmonary ventilation is open to question, since expiration automatically follows pulmonary inflation. A beneficial effect on pulmonary circulation which remains to be demonstrated may accompany the pumping action.

It was suction or high negative pressure that produced the pulmonary edema and hemorrhage associated with the employment of the old pulmotor. It is obstruction of the tracheal airway by edema of the lining membrane that sets in operation a vicious cycle to transform respiratory effort into suction, so that the lungs are filled with fluid from the blood stream instead of air from the ambient atmosphere.

To counteract the tendency to edema Barach has employed positive pulmonary pressures of 5 to 8 cm. of water. It is this important therapeutic principle that can be utilized in the treatment of casualties from gas poisoning.

Pulmonary Gas Pressures

If the native diver returns to the surface the compressed air will leave the sinal and aural spaces and the diminished thoracic volume will return to its initial value. Symptoms referable to the ears and sinuses rarely attend rapid decompression. If mucus, how-

ever, prevents the egress of air from a frontal sinus, pain is again a concomitant symptom of the differential pressure, which, being greater in the air space, now acts to compress the lining membrane.

If decompression of the diver is continued further by a flight to high altitude it is observed that at a level of 5,000 feet pulse rate may increase slightly. During brief exposures, however, no real disturbances are to be anticipated until a "ceiling", usually in excess of 12,000 feet, is reached. In military aircraft oxygen would be inhaled, but since we are interested in physiologic responses, the diver will be taken to 18,000 feet, breathing air. This altitude is a critical level where the oxygen pressure is too low to support continued existence even in thoroughly acclimatized individuals, or to maintain the proper functional response necessary for the safe operation of aircraft.

Although the aviator may be on guard against untoward symptoms, the unsuspecting native diver will be unaware that he possesses faulty judgment and impaired neuromuscular coordination, especially if his mood becomes euphoric. The common anoxic symptoms of a darkening and narrowing of the field of vision and a feeling of cold may not disturb our now nonchalant diver.

The inhalation of oxygen, however, will tend to reverse the symptoms and restore the diver to normal well-being. Altitude ascent now may safely continue to 34,000 feet, equivalent to 0.25 atmosphere. The total gaseous pressure in the lungs, 190 mm. of mercury, will be the sum of the partial pressure of the three gases (water vapor, 47 mm. of mercury; carbon dioxide, 40 mm. of mercury; and oxygen, 103 mm. of mercury), or essentially the same corresponding gas pressures that exist in the lungs as we breathe air at normal pressure.

It is of interest that the replacement of air by pure oxygen is not attended at this reduced pressure by those toxic effects referable to the lungs and nervous system when pure oxygen is inhaled in the high pressure chamber. Our divers, insofar as the pulmonary gas pressures are concerned, are capable of carrying on the same type of respiratory function that attends the respiration of air at sea level.

Overdistention of Abdominal Viscera

At an altitude of 34,000 feet further ascent may be limited by previously compressed gases present in the stomach and large intestine which make their presence felt in no uncertain manner. Our native diver may be impelled to seek relief by way of a parachute descent.

An appreciation of the type of difficulty associated with gaseous distention is afforded by an experiment at ground level in which helium was introduced into the duodenum. It required two liters of retained helium to produce sensations similar to those sometimes encountered at a simulated altitude of 38,000 feet. Roentgenographic examination revealed the movement of the gas from the duodenum into the large bowel within a period of forty-five minutes.

A viscus distended with gas loses much of its functional motility. In distention of the stomach, for example, the cardiac and pyloric sphincters retain their gas-tight integrity to render an individual helpless and to create a condition of imminent rupture of the gastric wall. It is this fact that endows a seemingly innocent condition with distressing and fearful potentiality.

The visceral gas arises not primarily from the digestion of food, but from swallowed air. In the experimental development of helium-oxygen diving the project was almost abandoned before it was recognized that in the use of a mouthpiece for helium respiration large quantities of gas were swallowed. During decompression the rapid expansion of the ingested gas caused intense griping pain which at first was misinterpreted as a sign of compressed air illness. The substitution of a mask or helmet for the mouthpiece eliminated the excessive salivation and concomitant gas-swallowing.

Efforts toward the prevention of gaseous distention are directed largely to limitation of air swallowing and eating prior to flight. In this regard, without partiality, it can be stated that chewing gum and not tobacco is an offending agent.

Clinically gaseous distention following operative procedures is recognized as a distressing problem. One of the therapeutic measures recently advocated is the inhalation of oxygen. It is likely that the value of oxygen inhalation lies not so much in the elimination of gaseous nitrogen by way of the blood stream but rather in the fact that swallowing during oxygen inhalation introduces readily absorbed gas in contrast with

the accumulating nitrogen which depends for its elimination upon intestinal motility.

The Problem of Aero-Embolism

The more familiar phenomena resulting from compression and decompression are related to the formation of gas bubbles in the blood stream.

Robert Boyle (in 1670) first observed the tendency of bubbles to form in the blood during rapid decompression. He reported a remarkable observation—namely, the presence of a bubble in the eye of a viper subjected to low pressure. Boyle, moreover, outlined what appears to be the true nature of compressed air illness in the following statements quoted from the paper of Professor John Fulton:

"The little Bubbles generated upon the absence of the Air in the Bloud, juyces, and soft parts of the Body, may by their Vast number, and their conspiring distention, variously streighten in some places, and stretch in others, the Vessels, especially the smaller ones, that convey the Bloud and Nourishment; and so by choaking up some passages, and vitiating the figure of others, disturbe or hinder the due circulation of the Bloud!"

Boyle's observations apparently were not recalled at a later date when the maladies following exposure of divers and compressed air workers were explained on the philosophically plausible hypothesis that compression acted to squeeze blood into the interior of the body and that decompression was followed by an injurious reactive hyperemia.

Then Paul Bert, in 1878, with the perspicacity that distinguished the brilliant French scientists, presented experimental proof of the relationship between air embolism and decompression symptoms in his classic book, LA PRESSION BAROMETRIQUE.

The use of recompression in the treatment of compressed air illness is but the application of Paul Bert's theory. Perhaps no therapeutic procedure is more effective than recompression in the treatment of the asphyxiated, pulseless, cyanotic patient whose blood stream is filled with multiple gas emboli.

In anesthetized dogs rapidly decompressed the accumulation of gas bubbles in the right ventricle and pulmonary capillary bed is associated with rapid, shallow breathing, a fall in blood pressure, and a slow heart rate (fig. 8). The severity of the asphyxia is evident

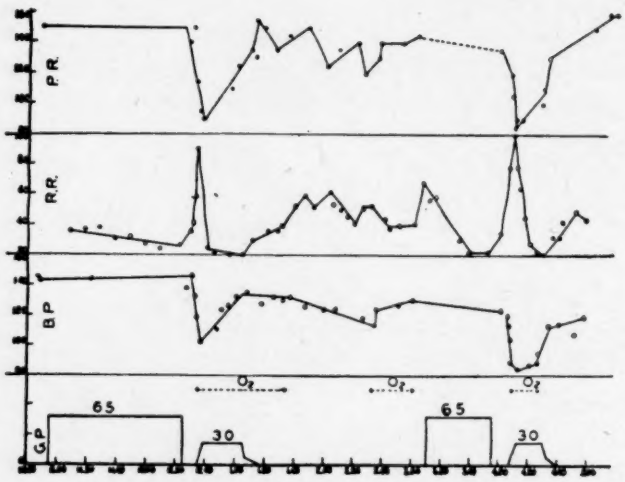

Fig. 8. Alterations in blood pressure, respiratory rate, and pulse rate of a dog decompressed in 10 seconds from a gauge pressure of 65 pounds after 1.5 hours' exposure, and then recompressed (after an interval of 10 minutes) to a pressure of 30 pounds (oxygen) for 25 minutes. Pressure was then lowered to atmospheric in 12 minutes, and oxygen inhalation continued for 17 minutes. Preceded by a period of oxygen breathing (30 minutes), compression of the dog was again carried out at a pressure of 65 pounds for a period of 45 minutes, followed by a 10-second decompression. After an interval of 12 minutes the dog was recompressed to a pressure of 30 pounds for 20 minutes (oxygen inhalation). From Behnke and Shaw: Use of Oxygen in the Treatment of Compressed Air Illness, U. S. Nav. M. Bull. 35:61-73 (Jan.) 1937.

from analysis of the oxygen content of arterial blood, which may be reduced to one-third of the initial value. The belief that gas bubbles interfering with blood flow in the pulmonary vascular bed induce the asphyxia is substantiated by the disappearance of the symptoms during the period of recompression.

In man we may, with reasonable assurance, assume that the mechanism of "chokes" is the same as that which causes asphyxiation in the dog. The rapid, shallow breathing, sometimes mistaken as a symptom of oxygen poisoning, has been observed in the rapidly decompressed diver.

Not all "chokes", however, are severe, and a mild form is of especial interest. About ten years ago routine exposure in the high pressure chamber was not infrequently followed, after several hours, by the rather abrupt onset of substernal distress characterized by a sensation of dryness and burning that accompanied or induced a shallow type of breathing. Habitual smokers were unable to inhale tobacco smoke. Deep inspiration aggravated the distress and elicited the

cough reflex. This reflex has proved to be an early sign of incipient "chokes" or asphyxia, not only after diving decompression but in aviation during simulated rapid ascents to high altitude. The inhalation of oxygen at ground level, or recompression in a chamber relieves the symptoms.

Of interest is the fatigue, specific in character, that frequently follows compression. It may occur as the only symptom to indicate borderline cases in which bubbles presumably are present, but not in sufficient number to elicit the pain response. In association with "bends", fatigue may take the form of an exhausting malaise combined with chills, fever, and sweating.

Are these symptoms the result of products of anoxic tissue destruction brought about by the embolic ischemia?

Paralysis constitutes the most serious complication of compressed air illness. The manifestations in man are similar to those observed in dogs, and indicate ischemic involvement and necrosis, particularly of the thoracolumbar segments of the spinal cord.

Of the minor symptoms pruritis and rash are indicative of bubbles in the cutaneous vessels.

The general picture of widespread liberation and circulation of gaseous emboli is essentially a deprivation of blood supply to tissue. In no other way can the protean symptoms of compressed air illness be explained—symptoms which can be made to appear or disappear in response to the ambient pressure environment.

Clinical entities producing symptoms similar to those associated with widespread embolism are the systemic diseases such as syphilis which injure blood vessels and deprive tissues of blood supply. The rash of compressed air illness, for example, is frequently a copper colored, macular eruption. The symptoms of tabes dorsalis may be reproduced by the changes following decompression embolism affecting the areas of spinal cord with poor blood supply, predominantly those in the lower thoracic and upper lumbar portions.

Reichert and others described the condition of four patients with extensive arteriosclerosis of the lumbar segmental arteries who exhibited weakness of the thighs on exertion, not accompanied by pain and associated with normal pulsation of the femoral arteries. A similar syndrome was produced in dogs by ligation of the lumbar segmental arteries. Thus, interference with the blood supply to tissues by decompression embolism in young, healthy men simulates the symptoms associated with the aged or with individuals afflicted with arteriosclerosis and other forms of systemic vascular disease.

The incipient lesions incident to ischemia induced by decompression embolism fortunately disappear rapidly if blood supply is promptly restored by the application of adequate recompression.

Compressed Air Illness in Relation to High Altitude Flight

Of the factors involved in aerial supremacy the ability to reach and maintain high altitudes may be decisive. Not only have fighter aircraft climbed at the rate of a mile a minute to reach altitudes above 30,000 feet, but bombers also have attained altitudes beyond the reach of ground anti-aircraft batteries. In contrast to night saturation bombings carried out at comparatively low altitudes are the precise high altitude daytime operations of the American air fortresses—one of the most demoralizing methods of attack yet introduced into the war.

What of the individual who has been suddenly transferred from the normal pressure environment to the partial vacuum of the substratosphere? In effect he has been suddenly decompressed and it is not surprising that his symptoms appear indistinguishable from those experienced by the deep-sea diver who is decompressed too rapidly.

Some two years ago our deep-sea divers at the Experimental Diving Unit were subjected to a rapid rarefaction of air in the pressure chamber, simulating the aviator's flight into the substratosphere at the rate of 5,000 feet per minute. Above 27,000 feet the divers experienced the already familiar rash, fatigue, pain, and "chokes". To the divers there was no qualitative difference between the effects of too rapid decompression from a level of thirteen atmospheres and those changes brought about by the rapid, simulated altitude ascent, starting from a pressure of one atmosphere at ground level. The symptoms experienced at high altitude appear to be less severe, however, in that recovery is more prompt following descent.

Illustrative of the similarity of decompression symptoms, irrespective of the pressure

level, is the history of one individual who in 1933, following exposure to high pressures, felt a dull, aching type of pain in the deltoid area of the right arm accompanied by substernal distress which elicited the cough reflex on deep inspiration. In 1940, identical symptoms were manifest in the same individual following too rapid simulated altitude ascent to 38,500 feet.

Again, during one week a diver decompressed too rapidly from a pressure level of thirteen atmospheres (equivalent to a diving depth of 400 feet) was temporarily incapacitated by pain and swelling of both ankles. A dorsal pedal vein in one foot was distended, presumably because of the blockage of blood flow by gas bubbles. Prolonged recompression effected complete recovery. The following week the same diver, after rapid decompression from the normal barometric pressure to a simulated altitude of 38,000 feet, developed the same incapacitating ankle pain of the previous week.

Another diver who, during the course of several years of experimental diving, had been the only individual to escape "bends", developed "chokes" at a simulated altitude of 40,000 feet.

Finally, the irritability and fatigue that accompany too frequent exposure in compressed air are exhibited by those attendants who work too often either in the low or high pressure atmosphere.

With reference to the more rapid recovery characteristic of descent from high altitudes, it is probable that the greater water vapor and carbon dioxide content of the bubbles is responsible for the more rapid resolution of gas and disappearance of the obstructing emboli. On recompression the carbon dioxide and the water vapor would be expected to redissolve more rapidly than the more slowly absorbed nitrogen. Yet bubbles have not been demonstrated within the vascular beds and tissues of men subjected to high altitudes, and similar symptoms may not mean similar cause.

The removal of molecular nitrogen from the tissues of the body by oxygen inhalation prior to altitude flights or at the lower altitudes renders susceptible individuals resistant to decompression maladies which otherwise would bring about incapacitation during high altitude flying. This phenomenon constitutes the essential link in the proof that air embolism underlies the etiology of the decompression symptoms at high altitude. The rationale of nitrogen removal serves as an example of the value of physiologic principles as applied to naval operations.

Summary

Entrance into the pressure chamber reveals a physiologic world that in some respects presents the incongruity of the experiences of Alice in Wonderland. The phenomena, however, can be grouped into a rough pattern. Pressure alterations *per se*, equally distributed on all parts of the body, are innocuous in the range of sixteen to one-sixth atmospheres. If the pressure is unequally distributed tissues are squeezed to produce edema, hemorrhagic extravasation, and pain. For the production of these symptoms the pressure difference need not be more than 50 mm. of mercury.

The more profound disturbances associated with pressure alterations are related to the properties of gases. Under high pressures benign atmospheric nitrogen becomes a narcotic substance and vital oxygen is transformed into a convulsive agent.

During and following rapid decompression, gases in the lungs and alimentary tract expand to produce symptoms dependent upon the resultant overdistention. In the blood stream the dissolved gases may be liberated to form emboli which serve to explain the mutual symptoms of pain, asphyxia, irritability and fatigue affecting both the deep sea diver and the aviator.

Clinically, the pressure forces properly controlled have served to maintain respiration and to improve circulation. Further developments look to the employment of the pressure chamber not only as a diagnostic mechanism but also as an adjunct to promote ventilation and drainage in the treatment of aural, sinal and pulmonary infections. When these procedures are put into effect, military ecologic practice will have made a contribution to clinical medicine.

The third lecture in this series will be published in the April issue of the **North Carolina Medical Journal.**

Private initiative is responsible for America's world leadership in science and industry. The tremendous effort that is being put forth in the United States, the effort that will win the war, is the work of private initiative.—Dr. Gustav Egloff: Peacetime Values From a War Technology, Science 97:102 (Jan. 29) 1943.

THE HORMONAL APPROACH TO CARCINOMA OF THE PROSTATE

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PART I: HORMONES AND THE PROSTATE

The interrelationship of the testes, prostate and pituitary glands has long been recognized. Changes in the physiology of one cause alterations in the others, and these changes are evidenced by physiologic and anatomic variations in the individual. These glands are bound closely together by a mutual interdependence. Admittedly, there has been considerable conflicting evidence in experimental data on their hormonal relationships, but it is now generally recognized that hypophysectomy causes prostatic atrophy and that the injection of the anterior lobe hormone, antuitrin S, in the normal male causes prostatic enlargement. This atrophy after hypophysectomy may be prevented, however, by the administration of testosterone[1]. The pituitary gland normally is held in check by the gonadal hormones, and if the gonads are removed the pituitary becomes overactive. It is theorized that the male gonadal secretion contains two hormones—one, called "inhibin", which holds the pituitary in check and, therefore, prevents the over-stimulation of the prostate; and a second, an androgen, which is the true sex hormone. It maintains the prostate and may cause prostatic hyperplasia. It is reasonable, therefore, to assume that dysfunction of either of these hormones may cause prostatic enlargement. It is also known that large doses of testosterone will not prevent the over-action of the pituitary gland. Therefore, it is theoretically unsound to administer, therapeutically, testosterone for prostatic hypertrophy. This mutual interdependence and interrelationship of these three glands still needs experimental investigation.

Androgens and the Prostate

The relationship between the testes and the prostate has been the subject for much experimentation and dispute. In 1893 White pointed out that prostatic atrophy follows castration. At that time oophorectomy was the accepted treatment for myoma of the uterus and White applied this principle to analogous conditions of the prostate. He claimed that 87 per cent of his patients with prostatic enlargement were improved by castration. Others, however, did not report such encouraging results. Experimentally there has been conflicting evidence. Deming, Jenkins and Van Wagenen[2] could find no evidence in the rat of prostatic atrophy after castration. One of their patients with benign prostatic hypertrophy was a man who had had both testes destroyed accidentally in his youth. This condition, however, is rare, as most eunuchs have small, soft, atrophic prostates, even in old age. Krichesky[3] has recently shown by the use of intra-ocular prostatic implants the relationship between the prostate and the testes. He concludes that the same result is obtained in his implants by castration or injection of testosterone. In prostatectomized castrated animals the injection of testosterone causes rapid and continued growth of the implant, while in prostatectomized animals with testes the injection causes only a slight temporary rise and then a continual decrease in size of the prostatic implants. This suggests that the testes secrete a hormone which inhibits the action of the androgen on the prostate. Whether this action is direct or indirect through the hypophysis is not shown. This falls in line with Lower's theory of inhibin. The relation of age to male hormonal secretion has been investigated by many. Womack and Koch[4] and others have shown that in boys under 10 years of age there is no male hormonal secretion found in the urine; between the ages of 20 and 40 there is the greatest amount; between 40 and 60 there is just half as much as in the preceding group; and after 60 years there is very little. Huggins and Clark[5] have shown that castration produces atrophy of the normal prostate of dogs. It also causes

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From the Urologic Division, Department of Surgery, Duke University Medical School and Duke Hospital.

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2. Deming, C. L., Jenkins, R. H., and van Wagenen, G.: Further Studies in the Endocrinological Relationships of Prostatic Hypertrophy, J. Urol. 34:678-685 (Dec.) 1935.
3. Krichesky, B., et al: Endocrinologic Studies on the Prostate Gland in the Male Rabbit, J. Urol. 46:303-318 (Aug.) 1941.
4. Womack, E. B., and Koch, F. C.: Testicular Hormone Content of Human Urine, Endocrinology 16:273-277 (May-June) 1932.
5. Huggins, C., and Clark, P. J.: The Effect of Castration and of Estrogen Injection on the Normal and on the Hyperplastic Prostate Glands of Dogs, J. Exper. Med. 72:747-762 (Dec.) 1940.

atrophy in prostatic hyperplasia, but this may not become apparent until three months after castration. They feel that this apparent discrepancy in their findings from those of others is dependent upon the fact that it takes three months for the epithelial atrophy to become evident. Perhaps others have not carried their experiments long enough for this atrophy to become evident. They have shown that prostatic epithelium is under the control of the testes[6]. If these are true facts, injection of the male hormone in prostatic hypertrophy is certainly contraindicated.

Estrogens and the Prostate

The effect of the female sex hormones on prostatic hypertrophy has been investigated by many. Zuckerman and others have demonstrated that the male secretes both androgenic and estrogenic hormones in the urine. There is a balance between the two in every male. If the estrogen is withdrawn, as perhaps it is in old age, the androgen is not kept under control and its preponderance stimulates the pituitary to over-secretion of its hormone, which in turn causes prostatic enlargement. Thus the enlargement is caused by the deficiency of one of the hormones and a consequent relative increase in the other, its antagonist. Wugmeister in 1937 reported marked improvement in 23 cases of benign prostatic hypertrophy treated with estrogen. He theorized that the female hormone is present in every male but is withdrawn in later life. The individual, either male or female, tends toward hypervirilization. The pituitary, no longer inhibited by the estrogen, begins over-production of gonadotropic hormones which stimulate the genital glandular apparatus. The glandular tissue responding most actively to this stimulation is the peri-urethral glands, which have remained embryologically at an inferior stage of evolution. Kahle and Maltry[7] had results similar to those of Wugmeister in patients on stilbestrol therapy. Huggins[5] has induced prostatic atrophy in dogs by injections of stilbestrol. However, an overdose may cause metaplasia and enlargement. On this subject reports have been conflicting, one group of experimenters finding a decrease and another group an increase in the size of the prostates of different animals given estrogenic injections. Geschickter said that a moderate dose caused enlargement of the prostate while a large dose caused atrophy. The differences reported may also be dependent upon the various animals used for experimentation.

Castration and Carcinoma of the Prostate

While there is some question as to the result of castration in benign prostatic tumors, there is no doubt at all that it causes atrophy of the prostatic epithelium in carcinoma of the prostate. Huggins[5], Gutman[8], Gomori[9] and others have shown that carcinoma of the prostate is a tumor of adult prostatic epithelium by the similarity in the staining reactions and the high tissue acid phosphatase in each. In primitive prostatic epithelium, on the other hand, there is very little acid phosphatase. Acid phosphatase may be considered, therefore, as an index of adult prostatic epithelial activity.

The endocrine control of adult prostatic epithelium is best shown by the withdrawal or neutralization of the androgens by castration or stilbestrol. Since 1896 the relationship between carcinoma of the breast and the endocrines has been known. Oophorectomy was beneficial, particularly in the carcinomas with osseous metastases. Recently Woodard and Higinbotham[10] have shown that testosterone or estrone causes stimulation of neoplastic growth in carcinoma of the breast, with metastases and increased bone destruction. The products of these osteolytic changes are evidenced in the blood by the elevation of the serum calcium. The androgenic relationship of the phosphatase is not the same in carcinoma of the breast and carcinoma of the prostate. There is now abundant evidence that removal or neutralization of the androgen causes rapid and marked atrophy of the adult epithelium of prostatic carcinoma.

In our series[11] of forty patients who had been castrated, almost every prostate showed

6. *Huggins, C., and Stevens, R. A.: The Effect of Castration* on Benign Hypertrophy of the Prostate in Man, J. Urol. 43:705-714 (May) 1940.
7. *Kahle, P. J., and Maltry, E.: Treatment of Hyperplasia* of the Prostate with Diethylstilbestrol and Diethylstilbestrol Dipropionate, New Orleans M. & S. J. 93:121-131 (Sept.) 1940.
8. *Gutman, E. B., Sproul, E. E., and Gutman, A. B.: Significance* of Increased Phosphatase Activity of Bone at the Site of Osteoplastic Metastases Secondary to Carcinoma *of the Prostate, Am. J. Cancer 28:485-495 (Nov.) 1936.*
9. Gomori, G.: Distribution of Acid Phosphatase in the Tissues Under Normal and Under Pathologic Conditions, Arch. Path. 32:189-199 (Aug.) 1941.
10. Woodard, H. Q., and Higinbotham, N. L.: Correlation *Between Serum Phosphatase and Roentgenographic Type* in Bone Disease, Am. J. Cancer 31:221-237 (Oct.) 1937.
11. Alyea, E. P., and Henderson, A. F.: Castration for Carcinoma of the Prostate, J. Urol. 48:673-681 (Dec.) 1942.

marked atrophy and softening. So marked was the change that many cases could not have been diagnosed as carcinoma by rectal examination four months after operation. Two of seven patients with acute retention had already had a suprapubic cystotomy for relief. The glands of all seven atrophied to such an extent that their retention was completely relieved and the two suprapubic sinuses healed. The latter fact, particularly, shows that all obstruction must have been removed. Rectal examination corroborated this assumption. Since castration was the only therapy in these 7 cases, the relief of the obstruction must have been dependent upon the removal of the androgens.

This definite relationship between androgens and carcinoma of the prostate has stimulated investigation of the true male hormones in the urine. Both androgens and estrogens are present in the human urine. It was thought that the 17-ketosteroid was the male hormone. Estrogens giving the reaction of these steroids are usually found in the phenolic fraction and androgens in the neutral fraction. Assays of these substances in the urine are taken as an index of the presence of the androgens. These are not altogether reliable, for some 17-ketosteroids in the neutral fraction have no androgenic properties in biological assays. Therefore, a quantitative determination of the 17-ketosteroids in the urine is not a true index of the quantitative androgenic hormone in an individual.

If benign prostatic hypertrophy is caused by an abnormal ratio of the estrogens and androgens, this abnormality should be demonstrated by a determination of these substances in the urine of patients with this condition. Satterthwaite and his co-workers[12] and Miller[13] have determined the 17-ketosteroids in the urine of normal old men and in that of men with benign and malignant tumors of the prostate. They found no consistent difference in the three groups. Furthermore, it has been demonstrated that the testes are not the only source of the 17-ketosteroids. They are also secreted by the adrenals. This fact is evident after castration. Satterthwaite found a decrease after castration, but others have found a temporary drop followed by a rise, which in some cases surpassed the precastration level. These 17-ketosteroids must have been produced by extragonadal sources. Scott and Vermeulen[14] found that the urinary hormonal levels are the same in a normal male, in patients with carcinoma of the prostate, and in eunuchs. After castration there is a temporary fall of these hormones, then a rise to precastration levels. We must conclude, therefore, that castration causes primary gonadal insufficiency, but only moderate changes in the urinary excretion of the gonadotropins, androgens or estrogens. Hence, a determination of these hormones in the urine cannot be regarded as evidence of functional capacity of the gonads.

A most interesting and curious syndrome has been described in the foreign literature. In 1925 Corda[15], and a year later Silvestrini[16], described gynecomastia and atrophy of the testes in patients with extensive or chronic disease of the liver. Corda implied that this syndrome was in some way dependent upon the endocrines. Zondek[17] in 1934 introduced the theory that the liver inactivates the female sex hormones. Glass et al[18] stated that there is now ample experimental proof of such a mechanism. They studied fourteen males with primary chronic liver disease; eight had gynecomastia, and all had testicular atrophy. According to them, most investigators have found little free androgen or estrogen in *normal* urine. Hence, the recovery of these sex steroids in the free rather than in the combined form may be considered as evidence of liver failure to inactivate these compounds. They found low androgens in all of the 14 cases of cirrhosis. In 8 patients they recovered the free estrogen in the urine. This, they think, indicates that inactivation did not take place. The greatest importance is placed upon the fact that the estrogens were found, in the cases of cirrhosis of the liver, in the free form. Thus, in

12. Satterthwaite, R. W., Hill, J. H., and Packard, E. F.: Experimental and Clinical Evidence on the Role of the *17 Keto-Steroids in Prostatic Carcinoma, J. Urol. 46:1149-1153* (Dec.) 1941.
13. Miller, M. L.: Neutral Steroids in the Urine of Individuals with Benign Hypertrophy of Prostate, *J. Urol. 47:* 846-851 (June) 1942.
14. Scott, W. W. and Vermeulen, C.: Excretion of 17 Ketosteroids, Estrogens and Gonadotropins Before and After *Castration, J. Clin. Endocrinol. 2:450-456 (July) 1942.*
15. Corda, L.: Sulla c. d. reviviscenza della mammella maschile nella cirrosi epatica, Minerva med. 5:1067-1069 1925.
16. Silvestrini, R.: Gynecomastia in Men with Cirrhosis of the *Liver, Riforma med. 42:701-704 (July 26) 1926.*
17. Zondek, B.: Ueber das Schicksal des Follikelhormons (Follikulin) im Organismus, Skandinav. Arch. f. Physiol. 70:133-167, 1934.
18. Glass, S. J., Edmondson, H. A., and Soll, S. N.: Sex *Hormone Changes Associated with Liver Disease, Endo*crinology, 27:749-752 (Nov.) 1940.

this active biologic form they can be more potent in relatively lower concentration.

Wu[19] has undertaken a morphologic study of the prostates of patients with cirrhosis of the liver in an attempt to show characteristic changes due to estrogenic preponderance. In a small series he found a higher incidence of nodular hyperplasia and delayed involution in elderly patients suffering from cirrhosis of the liver. These findings are all evidence of estrogenic preponderance and suggest that the diseased liver is unable to inactivate the estrogens. If this is so, then, in the light of the new estrogenic therapy for carcinoma of the prostate, should there not be a lower incidence of this malignancy in old men with cirrhosis of the liver than in those with normal livers which inactivate the estrogens? This possibility will be investigated.

Phosphatase and Carcinoma of the Prostate

The previously mentioned investigations of Huggins have stimulated further studies of the relationship of the phosphatase enzymes to prostatic tumors. In 1912 Grosser and Husler[20] discovered an enzyme capable of hydrolizing phosphoric esters. There are many of these esters which have real significance in the metabolic processes of the body. The only two with which we are concerned in this paper are the alkaline phosphatase, most active in a medium with a pH of 9, and the acid phosphatase, most active in a medium with a pH of 5. According to Woodard[21], normal bone produces an enzyme which permits the organic phosphorus compounds to produce a local excess of inorganic phosphate, for deposition as calcium phosphate. Some bone tumors contain little or no phosphatase and therefore lack the ability to lay down calcium phosphate. Irradiation of the epiphyses inactivates the phosphatase producing mechanism.

In 1923 Robinson[22] discovered that the alkaline phosphatase was particularly active in growing bone and cartilage. Growing bone contains ten times as much phosphatase as adult bone; and the enzyme activity affords a good index of the rate of growth. This phosphatase is found also in many body tissues, particularly the kidneys and intestinal mucosa. In certain conditions—namely, obstructive jaundice and bone diseases, particularly giant cell tumors, osteitis deformans, osteoporosis, rickets, hyperparathyroidism, and osteogenic sarcoma it is markedly elevated in the blood serum.

Acid phosphatase, which is most active in an acid medium with a pH of 5, has been demonstrated histochemically by Gomori[9], in fairly large amounts in the spleen, smaller amounts in the liver, intestines, kidneys and adrenals, but in greatest amount in adult prostatic epithelium. The exact role of this enzyme in the prostate is not known, but it appears normally in prostatic fluid. Scott and Huggins[23] have reported that a high urinary acid phosphatase depends upon its admixture with prostatic secretion, and may be considered an index of the secretion, and hence also of prostatic activity. Sullivan and his co-workers[24] have given us a most excellent comprehensive study of the theory and application of this enzyme. They assume that its secretion is one of the functions of the prostate gland in man and monkeys, but not in other animals. The normal amount in the adult human prostate varies from 500 to 2,500 King and Armstrong units per gram of tissue. It has been shown by staining *in situ* and by chemical determination that acid phosphatase is abundant in adult type prostatic epithelium and scant in primitive type epithelium. Since it is most abundant in the glandular epithelium of patients with carcinoma of the prostate, it is assumed that this tumor is one of adult type epithelium. Further, since it does not appear in these prostatic cells until maturity, it may be taken as an indication of physiological maturity of the prostate gland. Gutman, Sproul and Gutman[8] have shown that there is a very high content of acid phosphatase in the metastatic lesions of prostatic cancer, particularly in the bone metastases. Later Gutman and Gutman[25] demonstrated an increase in the

19. Wu, S. D.: Anatomic Changes in the Prostate of Patients with Cirrhosis of the Liver, Arch. Path. 34:735, 1942.
20. Grosser, P., and Husler, J.: Ueber das Vorkommen einer Glycerophosphotase in tierischen Organen, Biochem. Ztschr. 39:1-5, 1912.
21. Woodard, H. Q., and Higinbotham, N. L.: Serum and Tissue Phosphatase Determinations as an Aid in Evaluating the Radiation Therapy of Bone Tumors, J.A.M.A. 116:1621-1627 (April 12) 1941.
22. Robinson, R. and Soames, K. M.: The Possible Significance of Hexosephosphoric Esters in Ossification, Bio-Chem. J. 17:286, 1923.
23. Scott, W. W. and Huggins, C.: The Acid Phosphatase Activity of Human Urine, an Index of Prostatic Secretion, Endocrinology 30:107-112 (Jan.) 1942.
24. Sullivan, T. L., Gutman, E. B., and Gutman, A. B.: Theory and Application of the Serum Acid Phosphatase Determination in Metastasizing Prostatic Carcinoma; Early Effects of Castration, J. Urol. 48:426-458 (Oct.) 1942.
25. Gutman, A. B., and Gutman, E. B.: An "Acid" Phosphatase Occurring in the Serum of Patients with Metastasizing Carcinoma of the Prostate Gland, J. Clin. Investigation 17:473-478 (July) 1938.

serum acid phosphatase of patients with metastatic carcinoma of the prostate. There are both alkaline and acid phosphatases in the serum of patients with metastases from prostatic carcinoma. In primary bone tumors the enzyme comes from the activity of the tumor itself. Therefore, if it is removed or irradiated, the serum phosphatase will drop. But in tumors of the soft parts which metastasize to bone, the enzyme comes from the defense, or bone, reaction to the tumor[26]. Hence, in carcinoma of the prostate where there is marked osteoplastic reaction to the tumor, the acid phosphatase is most active and elevated in the serum. The more osteoplastic the tumor, the higher is the serum acid phosphatase. In osteolytic lesions, however, the acid phosphatase rises only slightly.

The lack of agreement among investigators as to the normal level of serum acid phosphatase has lead to a great deal of confusion in the interpretation of clinical results. Sullivan, Gutman and Gutman[24] point out that the differences in laboratory techniques probably account for a good deal of this apparent discrepancy in values. The King and Armstrong method[27] is now probably the most widely accepted technique. Blood specimens must be examined fresh and not be allowed to stand at room temperature more than thirty minutes. Hemolyzed sera will give an abnormally high phosphatase. The variation in length of time of incubation also causes variation in the phosphatase value. The Gutmans chose three units as the highest level for normal, Herger[28] selected four units, and Huggins[29] ten units as the definite diagnostic dividing line.

In a series of 130 cases of carcinoma of the prostate with metastases Sullivan and Gutman[24] found that 85 per cent had serum acid phosphatase over 3 units, 75 per cent over 6 units, 50 per cent over 10 units. Of 240 patients with neoplasms other than carcinoma of the prostate, none had a phosphatase over 5 units. Of 85 patients with diseases of the prostate other than carcinoma, none had elevated acid phosphatase. In a control group of 570 patients with no prostatic disease 75.5 per cent had a serum acid phosphatase below 5 units. Herger and Sauer[28] reported that all of 283 controls had a serum acid phosphatase below 6 units. In 147 cases of carcinoma of the prostate, the serum acid phosphatase in 77 was below 4 units, and in 22 between 4 and 6 units. In 39 cases with metastasis to the bone 4 patients had a serum acid phosphatase below 4 units, 2 between 4 and 6 units, and 33 over 6 units. In our clinic, 5 units was chosen as the border line, and anything above that is considered as elevated and suggestive of carcinoma of the prostate. It is the general consensus of opinion that any value below 3 units is negative, that 3 to 6 units is suggestive, 6 to 10 units highly suggestive, and over 10 units almost certainly diagnostic of carcinoma of the prostate. It is thought that the tumor cells must escape outside the prostate itself and get into the circulation in order to cause a significant rise in the serum acid phosphatase. Sullivan and Gutman[24] have noted a normal phosphatase in a patient who at autopsy showed prostatic carcinoma with extension into the capsule, neural sheaths and perineural lymphatics. There was no further involvement or extension into the circulation of this patient, and his serum acid phosphatase was only 2.4 units.

The variations in the enzyme activity in metastasizing carcinoma depend upon "how prolifically the tumor elaborates the enzyme."[20] There are some cases reported in our series which did not show elevation of serum acid phosphatase on the first determination, but with further extension of metastases there was a gradual rise. These will be discussed in Part II of this paper. A certain percentage of cases of carcinoma of the prostate with metastases also fail to show the anticipated rise in serum acid phosphatase. No explanation is offered for this group at present. In an attempt to discover whether carcinoma of the prostate had metastasized in some of their cases with equivocal phosphatase values, Sullivan and Gutman[24] used a provocative test, as suggested by Huggins. Injection of androgen causes prostatic epithelial activation and a rise in the serum acid phosphatase if metastases are present. In some of their equivocal cases they produced the anticipated rise in serum phosphatase. There was no change in their control series of patients

26. Woodard, H. Q., Twombly, G. H., and Coley, B. L.: A Study of the Serum Phosphatase in Bone Disease, J. Clin. Investigation, 15:193-201 (March) 1936.

27. King, E. J., and Armstrong, A. R.: A Convenient Method for Determining Serum and Bile Phosphatase Activity, Canad. M. A. J. 31:376-381 (Oct.) 1934.

28. Herger, C. C., and Sauer, H. P.: Further Observation on Serum Acid Phosphatase Activity in Carcinoma of the Prostate, Cancer Research 2:398-400 (June) 1942.

with prostatic hypertrophy given the injection of testosterone.

Removal of Androgen and Serum Acid Phosphatase

Huggins and Hodges[29] have demonstrated that a decrease in serum acid phosphatase in metastasizing carcinoma of the prostate can be brought about by removal of the androgen, by castration, or by neutralization with estrogen. They also showed a rise in the serum acid phosphatase with the injection of the androgen. This experience has been confirmed in our cases[11]. In all of those patients with elevated acid phosphatase the level dropped to nearly normal and in those with normal amounts the level dropped still lower after castration or administration of stilbestrol. A few castrated patients, who, several months later, showed a spread of the disease and a rise of the acid phosphatase, were given stilbestrol, and the anticipated fall recurred. Theoretically, it is reasonable to assume, as has been suggested by Huggins, that the patients failing to respond or responding only temporarily may have excess secretion of extragonadal androgen, such as may be put out by the adrenals. This can be measured by the determination of the serum acid phosphatase. This chemical test is, therefore, of prognostic aid and a guide to therapy.

Sullivan, Gutman and Gutman[24] have shown that the fall in the acid phosphatase is rapid, 70 per cent occurring within the first week after castration. They also found a slight rise in the serum alkaline phosphatase two weeks following castration, and then a gradual fall to nearly normal levels.

This relationship between androgen, adult prostatic epithelium activation, and acid phosphatase is of the greatest significance. It is direct evidence of the relation of hormones to malignancy and may have far reaching results in the future. At present it is of the greatest value therapeutically in the care of patients with carcinoma of the prostate. A clinical report of our results with this therapy will constitute Part II of this study.

Summary

1. Hypophysectomy causes prostatic atrophy.
2. This atrophy may be prevented by testosterone injection.
3. Injection of antuitrin S causes prostatic enlargement if the testes are present.
4. Testicular hormone contains:
   a. "Inhibin", which holds the pituitary in check.
   b. Androgen, which maintains the prostate and may cause hyperplasia.
5. Castration will cause prostatic atrophy in the normal male.
6. Castration may cause atrophy of prostatic hyperplasia, although this is not definitely proved as yet.
7. Adult prostatic epithelium is under control of the testes.
8. Castration always causes atrophy of the adult prostatic epithelium of carcinoma of the prostate.
9. An imbalance of the estrogens and androgens may be the cause for prostatic enlargement.
10. Estrogenic therapy may cause atrophy of prostatic hyperplasia.
11. Estrogenic neutralization of the androgens causes atrophy of the adult prostatic epithelium of prostatic cancer.
12. The quantitative determination of 17-ketosteroids in the urine is not a true index of androgenic hormones of the individual.
13. Studies of cirrhosis of the liver seem to suggest that the liver inactivates the estrogens.
14. Acid phosphatase is found most extensively in adult prostatic epithelium and in cells of carcinoma of the prostate.
15. Serum acid phosphatase is elevated in metastatic carcinoma of the prostate.
16. Serum acid phosphatase rises with prostatic epithelium activation and falls with its inactivation.
17. Castration or neutralization of the androgens by estrogens causes a fall in the serum acid phosphatase.

29. Huggins, C., and Hodges, C. V.: The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate, Cancer Research 1:293-297 (April) 1941.

Gastrointestinal Upsets in Patients Taking Insulin.—Gastrointestinal upsets often are the precursors of a reaction. During such episodes, patients should always take some carbohydrate at frequent intervals, electing the form that can best be retained—tea or coffee with sugar, milk and Vichy water, ginger ale or similar preparations.—Elliott P. Joslin: Diabetic Hazards, New England J. Med. 224: 590 (April 3) 1941.

INFECTIOUS DISEASES OF THE HEART

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Infectious diseases of all kinds cause changes in the circulation which may be noted as abnormalities in the heart beat; infections of the heart itself produce manifestations varying with the portion of the heart involved. Pathologic changes in the myocardium usually result in acute symptoms associated with myocardial failure. Acute infection involving the endocardium causes few immediate symptoms; most of those which are seen are the result of late mechanical disturbances to the flow of blood through the heart. The symptoms and physical signs will depend upon the heart valve affected. For instance, changes are seen first in the peripheral circulation when the aortic valve is scarred; changes may be noted first in the lungs when the mitral valve is narrowed. Infections involving the pericardium cause few symptoms except pain in the acute stage, unless there is effusion, in which case the signs of mechanical obstruction to the venous return become evident.. Late effects produced by scarring give mechanical changes with a resulting constriction of the pericardium about the great vessels, or symptoms of diminished output if the constriction is around the ventricle.

It is perhaps better to consider the infections from an etiological than from a pathological viewpoint, since the prognosis and treatment will be more greatly affected by the former factor.

1. *Rheumatic fever.* The most important infectious disease of the heart is rheumatic fever. The disease rarely, if ever, occurs before the age of 2 years and is rare before the age of 5 years, but in the group under 20 years of age rheumatic fever comprises nearly 95 per cent of all infectious diseases involving the heart. In children it is generally true that the heart is involved more seriously than are the joints, while in the older age group the joints are more frequently involved than is the heart. We should recall that rheumatic fever is a generalized infection involving chiefly connective tissue wherever it may be found.

The etiology is still obscure. The occurrence of rheumatic fever following upper respiratory infections has led many observers to suspect a connection with bacterial infections of the upper respiratory tract. The presence of antibodies against the hemolytic streptococcus has been repeatedly demonstrated in patients with rheumatic fever, but this is certainly no proof that the disease is caused by this organism. Alpha hemolytic streptococci can be cultured from the blood stream of patients with rheumatic fever, if cultures are taken frequently enough and with large enough quantities of blood; but this organism may also be recovered from the blood of patients who have nothing more serious than pyorrhea if the cultures are taken while such patients are simply chewing paraffin. The flare-up of rheumatic symptoms seven to ten days after respiratory infections has suggested to many people that the disease represents an allergic response to some common organism or group of organisms. A virus has been postulated as the possible etiologic agent, but none has been constantly recovered. The frequent occurrence of rheumatic fever in tall, thin, blue-eyed, freckle-faced, red-headed individuals, and the tendency to repeated attacks in the same patient suggest a definite susceptibility on the part of certain individuals to the so-called "rheumatic state".

The disease may affect primarily the myocardium, in which case the only physical sign in the heart may be a muffled first sound, suggesting an increased P-R interval, which can be demonstrated by the electrocardiogram. The endocardium may be involved and the lesions may remain unsuspected until sufficient distortion of the valve has occurred to produce the tell-tale murmurs. The pericardium is almost always affected at some time during the course, but this lesion may be overshadowed by the involvement of the myocardium and endocardium. Involvement of the connective tissue around the joints may result in the familiar rheumatic nodules of the tendon sheaths seen most commonly around the elbows, or involvement of the pleura or the peritoneum may give a true rheumatic pleurisy or peritonitis. The incidence of the disease apparently is greatest in those climates where the weather is

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damp and cold, for the occurrence of rheumatic lesions at autopsy progressively diminishes in frequency from Boston to Baltimore and is lowest in New Orleans. Symptoms at this latitude may be mild and fleeting and the diagnosis may be difficult to establish during the acute stage. The white blood cell count, differential count, sedimentation rate and electrocardiogram are the only laboratory tests which will offer much help in making the diagnosis. In nearly all cases of rheumatic fever and in about half of all cases of chorea of rheumatic origin the heart is affected.

Since the etiologic agent is unknown, treatment must be entirely symptomatic. Salicylates in adequate dosage control the pain and reduce the fever but do not stop the underlying pathologic process. Salicylates tend to control exudation but not the proliferative lesions, so that in spite of the subsidence of symptoms the patient should stay quiet until objective laboratory evidence of activity of infection is no longer present. The sulfonamides have not proven effective in the treatment or prophylaxis of the disease. Removal to a warmer climate will often alleviate an attack and lower the incidence of recurrences.

2. *Syphilis.* In Negroes 25 to 30 per cent of all infectious diseases of the heart are due to syphilis. Males are more frequently affected than females. Syphilis is a septicemia in the early stage, and it is probable that the heart is involved to some extent in nearly all cases. The demonstration of the spirochetes in the myocardium is extremely difficult, however, except in the cases of congenital infection, where there may be myriads of organisms readily stainable in and between the myocardial fibers. The cardiac lesions seen in adults are found in the tertiary stage of the disease. Syphilis causes predominantly destruction of the media of arteries. The most common site of involvement in the heart is the aortic valve, and the development of the familiar separation of the cusps at their attachment results in insufficiency. There may be a diffuse inflammatory myocarditis, or more rarely, gummatous myocarditis, but some pathologists question the existence of these conditions. If the involvement of the media occurs near the mouth of the coronary arteries, the stage is set for the development of a therapeutic paradox in which there may be apparent improvement from vigorous initial therapy, but as treatment continues and healing progresses with scarring, the mouths of the coronaries become constricted and the patient develops signs of coronary insufficiency. If involvement of the heart is suspected, great care should be taken to initiate therapy with heavy metals and iodides and to continue this treatment for months before the arsenicals are started. The electrocardiogram may be helpful in detecting fibrosis by indicating disturbances in circulation to the heart.

3. *Toxins.* The heart may be affected severely as the result of damage from a circulating toxin produced by infection elsewhere in the body. The most frequent occurrence is in diphtheria. The patient usually is in the convalescent stage on the tenth or twelfth day after subsidence of the fever. The first physical sign noted may be a tachycardia with dilatation of the heart. Pathologically, there may be an acute myocardial necrosis with rapid or sudden death, but more frequently there is auriculoventricular or intraventricular block, which may be suspected from the muffled character of the first sound, indicating a delayed P-R interval, and which can be determined readily by an electrocardiographic tracing. The tachycardia is thought to be due to vagal and splanchnic paralysis caused by the circulating toxin. This infectious cause of damage to the heart should disappear, because the disease is preventable by proper prophylactic immunization and the myocardial lesions are preventable if adequate antitoxin therapy is instituted immediately on making the diagnosis. As a rule recovery from the myocarditis is complete, and if the patient survives the first four to six weeks, late effects of the disease need not be anticipated.

Myocardial damage rarely follows cases of scarlet fever. There is some evidence that this condition may be simply reactivation of quiescent rheumatic fever in a patient with the "rheumatic state".

4. *Less common infections.* Tuberculosis occasionally involves the heart, usually as a pericarditis originating by direct extension from caseous mediastinal nodes. The typical patient is a colored male, aged 40. The disease frequently is fatal, although recovery may occur, with adhesion or constriction of the pericardium. Tuberculosis and sarcoid

may very rarely cause a miliary myocarditis, with failure due to replacement of myocardial fibers by the infective granuloma. Occasionally, in typhoid fever, Zenker's degeneration of the myocardium occurs, although degeneration of the voluntary muscle of the abdominal wall is more frequent. Typhus fever, which is manifested chiefly as an arteriolitis with thrombosis and hemorrhage, may involve the myocardium.

5. *Rare diseases.* There is a group of rare diseases of unknown etiology which involve the heart. Among these is Libman-Sachs disease, which affects the endocardium with production of pink verrucous vegetations. This also affects the arterioles. Periarteritis nodosa and disseminated lupus erythematosus are other examples of primary arterial diseases which may involve the heart and which are probably infectious in origin, although this has not been proven.

6. *Tropical diseases.* Tropical parasitic diseases, particularly yellow fever and African trypanosomiasis, are said to involve the heart frequently. These will probably be seen more frequently after the present war when the soldiers who have been exposed to these diseases return.

7. *Secondary infections.* There is a large group of infections which are essentially septicemias, in which bacteria are discharged into the blood stream from a focus which has become secondarily engrafted on a previously damaged endocardium. The endocardium may have been damaged by congenital developmental abnormality, more commonly by a previous attack of rheumatic fever, and occasionally by the scarring of syphilis. The valves usually affected are, in this order, mitral, aortic and then those of the right side. Nearly every organism which causes disease in the human being has at some time or other been recovered from a patient with bacterial endocarditis. In one large series the alpha or green hemolytic streptococcus was recovered in slightly more than half the cases; the pneumococcus, staphylococcus and gonococcus each occurred in 10-15 per cent of the cases; and the other organisms were present in very small percentages. If sufficient care is taken with the bacteriologic studies, infections by two or more organisms can be found with surprising frequency. In the past this disease has proven almost universally fatal. The development of the sulfonamides, which tend to delay multiplication of the bacteria, offers our first hope of intelligently attacking the problem. Treatment will depend upon the laboratory findings. The organisms should be tested *in vitro* to determine which of the drugs will be most effective and what concentration must be maintained to prevent growth. The use of bacterial antiserum will depend upon the level of antibodies in the patient's blood serum. The use of neoarsphenamine, alone or in combination with the sulfonamides, and the use of anticoagulants are still experimental. One type of the disease may be attacked surgically, if the infection is implanted on a patent ductus arteriosus.

8. *Intercurrent infections.* Infections in various places throughout the body rarely cause serious damage in an otherwise normal individual. If the heart has been previously damaged from any cause, whether by circulatory abnormality or previous infection, even a relatively minor upper respiratory infection may precipitate serious cardiac complications. Abnormalities of rhythm, particularly auricular fibrillation, or myocardial failure may occur. It is common for any intercurrent infection to reactivate quiescent rheumatic fever. If there is underlying disease of the coronary artery with an arteriosclerotic plaque causing a break in the intima, the stage is set for the development of a thrombus as the result of increased fibrinogen and other changes in the blood caused by the infection. Most people who die during the course of an infection—as, for example, pneumonia—die of peripheral circulatory collapse. This is not truly a disease of the heart itself, but is failure of the heart resulting from the disturbance in the systemic circuit. In such cases cardiac stimulants and digitalis will be of no avail.

Summary

The heart may be involved during the course of infectious diseases as the result of primary infection of the myocardium, endocardium or pericardium. There may be direct invasion of the heart by the infecting organism, or the effects may be due to a circulating toxin. The heart may be secondarily infected or may fail as the result of changes in the systemic circulation occurring during intercurrent infection.

CHALYBEATE SPRINGS MINERAL WATER

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The name chalybeate was derived from an ancient people, the Chalybes, of Pontus in Asia Minor, who were iron and steel workers. They often developed bluish discoloration of the skin from the handling of iron. Chalybeate waters contain approximately .9 grain of iron carbonate to every sixteen ounces of mineral, or 0.01 to 0.12 grain of iron oxide per liter of water. These springs contain moderate amounts of Epsom and Glauber's salts, common salt, sulfate of lime, and a large quantity of carbonic acid gas. Among the most famous chalybeate springs are those in Cornica, Taubridge, and Brighton in England; St. Moritz, Pyrmont, Wiesbaden, and Spa on the Continent; Saratoga, New York; Bedford, Pittsburg, and Brandywine, Pennsylvania. There are also several in the mountains of Virginia, and one in Harnett County, North Carolina.

The peculiar color of the mineral responsible for the iron content of these waters is due to an oxide of iron, the intensity of color depending upon the degree of oxidation that has taken place. The color may vary from white to brown, and the mineral is often found as a precipitate at the bottom of the container. A very dark color is due to a large quantity of limonite, which is easily transformed into iron carbonate by oxidation. Crystals of iron carbonate are usually found as granular masses.

The use of iron as a hematinic in patients with chronic bleeding, chlorosis, or other secondary anemias is well known. The ingestion of excess amounts tends to irritate the bowels and produce constipation.

Electricity that has been "freed from the bondage of wire transmission" is being used by General Electric engineers to study minute specimen invisible under the ordinary light microscope. This electricity, in the form of electrons, is shot from a small electron gun at a fluorescent screen 11 inches away, and similar to that used in a television set. The specimen is inserted between gun and screen and as the electrons pass through or around it, and are magnified, they form an image of the specimen on the screen.

This action takes place in a simplified electron microscope described by Dr. C. H. Bachman in a talk January 23 at Columbia University (New York) before a joint meeting of the American Physical Society and the American Society for X-Ray and Electron Diffraction.

The instrument, which can be plugged into the regular 110-volt a-c house circuit, is capable of producing images 10,000 times the size of the subject. Further enlargement of the picture can be made photographically up to 100,000 times the size of the original specimen, or better, if desired.

If a hair 1/100 of an inch across, were split lengthwise into 100 slivers, and 99 of these pieces were thrown away and the one remaining piece was split again into 100 similar pieces, each of these filaments, only 1/1,000,000 of an inch across, would stand out clearly in the G-E instrument.

"The magnifying power of the electron microscope was not selected to attempt an approach to the ultimate, but rather to provide an instrument useful to the solution of immediate war and post-war problems confronting the great majority of workers in this field. It is believed that to these workers, the relative simplicity and ease of operation of the instrument will appeal," Dr. Bachman explained.

The machine is expected to expand the use of electron microscopy in laboratories now engaged in war work and medical research—and eventually to find wide usage in high schools and colleges. Due to present priority requirements, the device will be available for use only in essential laboratories and war plants.

The device uses the relatively small electron waves instead of light waves because their shorter length makes it possible to study much smaller objects than could be achieved with visible light waves. Light travels in waves of about 1/42,000 of an inch in length, and objects must be at least half that long before they can be seen under the ordinary optical microscope. Prior to the electron microscope, when objects to be viewed were smaller than this, it was impossible to obtain sharp images, so that further useful magnification at that wave length became impractical.

The new microscope has an over-all height of 52 inches, and requires floor space of about two by three feet. The cabinet includes simple power supply, the mechanical vacuum pump, and an air-cooled, oil-diffusion high vacuum pump. A camera is provided for mounting on the front of the instrument for photographing reproduction when this feature is desired. The cabinet is mounted on castors for mobility, and weighs 600 pounds. No special facilities for operating the instrument are needed, and the unit includes the microscope proper and all auxiliaries.

Physically, the microscope has been designed for the convenience of the operator. The electron chamber is mounted horizontally, the eye piece at one end being at eye level for an operator seated before the instrument. The electron chamber is supplied with voltage and is evacuated from the end which extends into the cabinet. All controls are at the operator's fingertips. These include accelerating voltage, image intensity, the main vacuum valve, focus control, and the movement of the specimen. In effect, the operator is seated at a desk with a drawer beneath so that materials and notebooks are conveniently at hand.

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QUID PRO QUO?

To the medical student and the prospective medical student, the proposed plan of the government to give a complete medical *education, with all expenses and a handsome* bonus of fifty dollars a month for spending money paid from the apparently inexhaustible unbalanced budget of Uncle Sam, must sound like a fairy tale too good to be true. To the parents of would-be doctors, harassed by mounting expenses and the growing burden of taxes, the plan is suggestive of the *generosity of a super Uncle Bim Gump.*

It is only natural and right to consider, however, just what is expected in return for *this free education, and to wonder if it is* best for the student himself, for his future patients, for the cause of medical education, and for the country.

Under its present system, American medical education is unquestionably the best in the world. The long preliminary college training required by all medical schools provides a certain cultural background that a doctor needs. The struggle to get an education, though often requiring sacrifice on the part of the boy or his parents, means that that education will be appreciated. To curtail the preliminary training to fifteen months—in some cases even omitting the last year of high school—cheats the youngster out of an important part of the groundwork for his medical education. He is doubly cheated because he will have no opportunity to know what he has missed, and little incentive in the future to repair the loss. Some vague talk of making up for the defective preliminary training by future postgraduate work is as empty as a promise made during courtship to reform after marriage.

The young doctor will find the awakening that he must face in the aftermath of the war all the ruder by contrast with the financial security afforded during his school days. It does not take an economist or a prophet to foretell that either inflation or repudiation of our national debt must come when the war is over; and either may be followed by a depression that will make the last one a rosy dream. Sooner or later the young man must be faced by the choice of entering private practice "on his own", or of continuing to be cared for from the public treasury. If the former course is chosen—or allowed under postwar conditions—the going will be rougher by contrast with the sheltered life he led as a Government ward. If he takes the latter alternative—supposing there are enough taxpayers left to support all Government employees—there will be lacking the incentive to cultivate his medical talents to the utmost.

His future patients must pay the price—unless he is unusually ambitious—of a medical education curtailed at each end and designed primarily to prepare him for military service, in which women, children, and the old are of secondary or even tertiary importance. These patients may also miss the privilege of having a family doctor, interested in them as individuals rather than as impersonal problems.

Medical education in Germany has been set back fifty years since it has been controlled by the Nazi military machine. Do we have to follow Germany's example in order to win the war? It is inevitable that the telescoping of our medical courses, and the very obvious subordination of medical education to the strictly utilitarian program of providing the army and navy with doctors just as these forces are provided with tanks, planes and submarines, will lower medical

standards. It must be remembered that these standards can be lowered much more easily and quickly than they can be raised again.

The country itself must suffer in various ways. One of the least, but still to be considered, is the extra tax burden entailed. Government expenditures have assumed such astronomical figures that a few hundred millions more or less may seem negligible; but the ides of this March have reminded millions of taxpayers that something more than token payments are now being required of our citizens. For years there have been far more applicants than our medical schools could accommodate, ready and anxious to pay their way. This year, with the largest income the country has ever had, would certainly see more than enough good material to fill all our schools. All that is necessary is for these men to be deferred from the selective service draft until they have finished their medical training. The argument that many would use this as a means of escaping the draft is pure buncombe. To think that any young man in his right mind would undertake the long, hard medical course just in order to postpone military service is laughable.

The plan savors strongly of totalitarianism. It is a long step toward federal control of education. With eighty per cent of the medical graduates—all but the women and the physically unfit—in the employ of the Government after graduation, for an indefinite period, politically controlled medicine will be upon us, whether we like it or not.

In our fight for freedom, let us not forget the freedom of American medicine to maintain its high standards, which have made it the best in the world. The young man of America certainly should not be required to sell his educational birthright for a sorry mess of socialistic pottage. Let us hope that we will not have to witness the betrayal of our youth.

* * * *

HOSPITAL VISITORS

An editorial in the January issue of the *Rocky Mountain Medical Journal*[1] suggests that "one war measure which could well become universal, and which could be well left in its war-time status afterwards" is limitation of the number of visitors a hospital patient may have. Certainly all hospital personnel and most physicians will breathe a fervent "Amen" to the sentiments expressed in this editorial, which reads, in part, as follows:

"Except for the patient who is dangerously ill, or moribund, in which case the doctor has a 'No Visitors' sign on the door, it is usually the patient who asks the doctor if there isn't something he can do to keep out the constant stream of visitors.

"Mrs. Jones has had a baby or an operation. Mrs. Smith, who hasn't seen Mrs. Jones for two years, and who under ordinary circumstances wouldn't see her for two more years, is imbued, immediately upon hearing the news, with an uncontrollable impulse to 'visit' her. And Henry Brown, who has not been to Lodge for five years, is awakened from the first sleep he has had in several days by a visitation of the 'Sick Committee,' none of whom he knows personally, nor they him. The corridor side of the glass partition of the hospital nursery, in the evenings and on Sunday afternoons, is crowded four and five deep with people 'looking at the babies' and most or all of the nursery staff, instead of taking care of the babies, are occupied with getting them from their bassinets and exhibiting them.

"The unlimited admission of visitors to hospital patients is a pernicious thing even in normal times. They consume the time of nurses and other attendants which had better be given to patients. They add to the clatter and noise of institutions which, outside of certain types of industrial establishments, are already the noisiest places there are, when they should be the most quiet.

"Any one who is sick enough to be in a hospital, even in the late convalescent state, should be permitted to make the most of an opportunity to secure all the relaxation and rest he or she can get, and not be forced to act as host or hostess for a ten-day or two-week open house.

"The responsibility for the limitation of visitors should not be placed upon the patient, for obvious reasons. It should be assumed by the doctors, or better by the hospitals themselves, which would limit visitors to patients to the immediate members of the family. Except for an occasional case, patients would probably be very grateful."

1. Editorial, Rocky Mountain M. J. 40:16 (January) 1943.

THE DIAPHRAGMATIC FLEXURE

A recent article by John L. Kantor[1] discusses a condition which most clinicians must have observed in a number of patients, but which for the first time he describes as a clinical entity. In his article he applies the term "diaphragmatic flexure" to "an anatomical condition in which the splenic flexure is located directly under the left diaphragm." The x-ray criteria of this condition "were established arbitrarily as follows: The tip of the splenic flexure must lie one-half inch (1.25 cm.) or less from the diaphragm when measured vertically on any film taken in the prone posture following either a barium meal or an opaque enema."

Kantor has found this anomaly in 157 of 996 patients—an incidence of slightly more than 15 per cent. He has found that the frequency of occurrence is approximately the same in both sexes, but that the condition is more often found in the stocky type of individual than in the slender and that it is often associated with the redundant colon.

Clinically, Kantor has found that this anomaly does not always produce symptoms, nor are its manifestations constant in the same individual. In order for it to give rise to discomfort, it is necessary for the flexure to be distended by gas, and for the stomach or heart —or both—to be impinged upon by the distended flexure. It requires little imagination, however, to understand how easily either of these organs might be pressed upon by a distended high splenic flexure and how a spastic distal colon, constipation, a redundant colon, and rectal fissure or hemorrhoids might bring about this distention.

The principal symptom of the diaphragmatic flexure is heart burn, which occurred in 46 per cent of the patients in Kantor's series, as against only 19 per cent of those in a control group. He explains this symptom as being due to the pressure of the distended flexure on the stomach, which forces part of its contents into the esophagus.

Another symptom is precordial pressure or pain, often radiating down the arm in anginal fashion. Other cardiac symptoms are palpitation, extrasystoles, and dyspnea, especially after eating and on exertion.

In addition to these symptoms, the pressure on the diaphragm may cause a feeling of fulness or bloating after meals, with repeated belching. This adds to the distress by the air swallowing induced. The intestinal gas content is increased, with further pocketing under the diaphragm.

The treatment of this condition may well be anticipated by an understanding of its mechanism. According to Kantor, it may be placed under the heading of the three R's: Reassurance, Relaxation, and Re-education.

By way of reassurance, the patient's condition is explained to him and he is made to understand that his symptoms, while annoying, do not mean serious heart disease, cancer, or ulcer, and that no operative procedure is necessary.

He is told to cultivate, so far as possible, that equanimity which is so desirable for every one; to secure adequate rest and sleep, with restful week-ends and frequent brief vacations; and to avoid coarse, irritating, or gas-forming foods. Anti-spasmodics, such as atropine or belladonna, and hypnotics if necessary are often helpful.

The patient should be re-educated in the proper care of the colon. He should be taught to avoid drastic cathartics and irritating enemas and to substitute bulk-producing but smooth substances, with an abundance of water, especially before breakfast. Lying on the left side helps to prevent the regurgitation of irritating material into the esophagus. Activities involving body-bending after meals, and the wearing of tight belts or corsets should be avoided.

1. Kantor, John L.: The Diaphragmatic Flexure, Am. J. Roentgenol. 47:417-426 (March) 1942.

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THE NORTH CAROLINA SCHOOL OF PUBLIC HEALTH

Announcement has recently been made of a fellowship, made available by the W. K. Kellogg Foundation, through the United States Public Health Service, for training personnel in health education. The fact that the North Carolina School of Public Health has been chosen to provide this training is a recognition of the achievements of this school and a tribute to the remarkable strides it has made under the leadership of Dr. Milton J. Rosenau, Director, and Dr. Harold W. Brown, Dean. The school has already rendered a great service to the state and to the nation in time of peace, and its contribution to the expanded war-time program of preventive medicine will be invaluable.

CASE REPORTS

CLINICO-PATHOLOGICAL CONFERENCE

Charlotte Memorial Hospital

NOVEMBER 23, 1942

C. S. J. was admitted to the Morris Field hospital on September 18, 1942, with a complaint of discharge from the penis of one week's duration. The family history was non-contributory. The patient had had typhoid fever at the age of 10. He contracted gonorrhea in 1926 and again in 1941. Since 1941 he had had slight morning drip but apparently no other complications.

The patient was exposed on September 7, 1942, and on September 11 he first noticed a urethral discharge. Physical examination on admission showed no abnormalities except a profuse urethral discharge. The diagnosis was "Gonorrhea, acute." So far as was known, the patient had taken no sulfonamide prior to admission. He was given 5 Gm. of sulfathiazole by mouth on September 18. Three days later, on September 21, a smear for gonococci was positive and sulfathiazole, 1 Gm. four times daily, was started. After another three days, on September 24, the patient developed high fever and an elevated rash of the face and neck, accompanied by marked prostration, nausea, vomiting and pain with constriction in the chest. The leukocyte count was 26,650, with 98 per cent polymorphonuclears. At this time the patient had received 18 Gm. of sulfathiazole within seven days. Sulfathiazole was discontinued and fluids were forced by mouth. The rash gradually improved and the temperature fell gradually from 105 F. on September 24 to normal on September 27. On September 25, however, considerable swelling of the face and eyelids developed, and the patient had difficulty in breathing. On September 27 almost complete anuria developed. During the next thirty-six hours he passed only three ounces of concentrated urine. On September 29 the nonprotein nitrogen was 30 mg. per 100 cc. of blood; creatinine 1.5 mg. per 100 cc.; plasma protein 5.2 Gm. per 100 cc. (albumin 3.2 Gm., globulin 2.0 Gm.). The patient could not be catheterized because of multiple urethral strictures. He gradually became semi-comatose and developed moderate abdominal distention. A urologist was called in consultation. With great difficulty a no. 4 rubber catheter was placed in the bladder and left in place. On this date, September 29, the blood pressure was 140 systolic, 90 diastolic. The urine gave a 2 plus reaction for albumin, and contained sulfathiazole crystals and occasional red blood cells. Sulfathiazole crystals had been detected in the urine as early as September 25. The white blood cell count dropped steadily until September 26, when it was 18,500. On September 29 only one ounce of urine was obtained by catheter. On this date a pericardial friction rub was heard over the entire precordium. The patient became comatose on September 30 and died at 7:20 p.m. with a temperature of 100.4 F. His nonprotein nitrogen on the day of death was 35 mg. per 100 cc. of blood.

Discussion

DR. W. B. MAYER: From the evidence presented, it is safe to say that the patient had a gonococcal urethritis and urethral stricture. There is nothing in the record on which to base a diagnosis of gonococcal septicemia or endocarditis. The fever, rash, and leukocytosis which the patient developed on the sixth hospital day are typical of a drug reaction of the acquired sensitivity type.

It is very unlikely that the massive dose (5 Gm.) of sulfathiazole was responsible for this reaction, since it is used routinely in military hospitals without known untoward results. Reactions of this type only follow repeated doses or prolonged treatment. The earliest time of their occurrence is said to be between eight and ten days after the initial dose; however, there may be exceptions, and serious reactions have been described four or five days after the beginning of treatment, or even earlier if the patient has previously had the same drug. Since our patient had had an acute attack of gonorrhea in 1941, it is likely that he had received sulfonamide treatment at that time. Acquired hypersensitivity to sulfathiazole is estimated to occur in from 10 to 30 per cent of all patients treated.

Subsequent to this acute febrile reaction, the patient developed complications which in three or four days led to death. The most serious complication of sulfonamide therapy, anuria, which developed in our patient, is frequently related to gross mechanical blockage of the urinary tract by concretions of

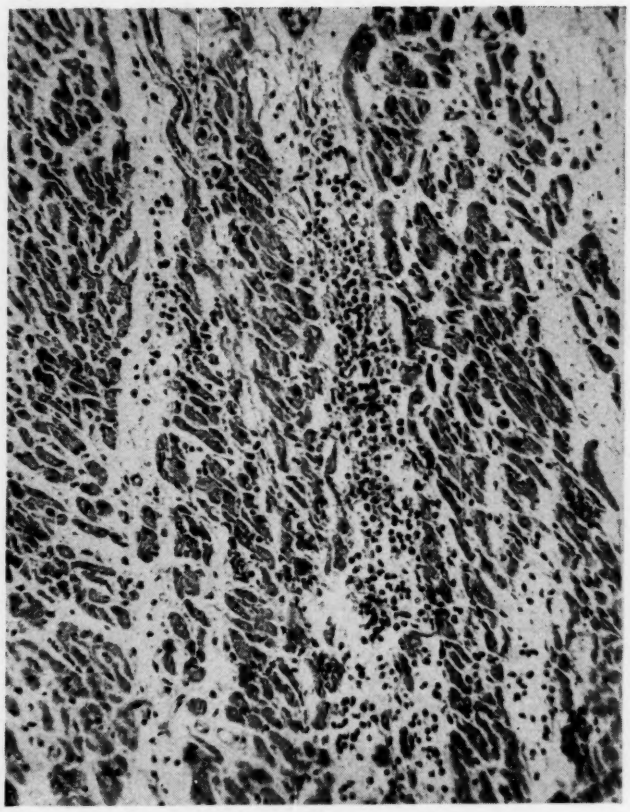

Fig. 1. Interstitial myocarditis, low power field, showing inflammatory infiltration in the interstices of myocardium.

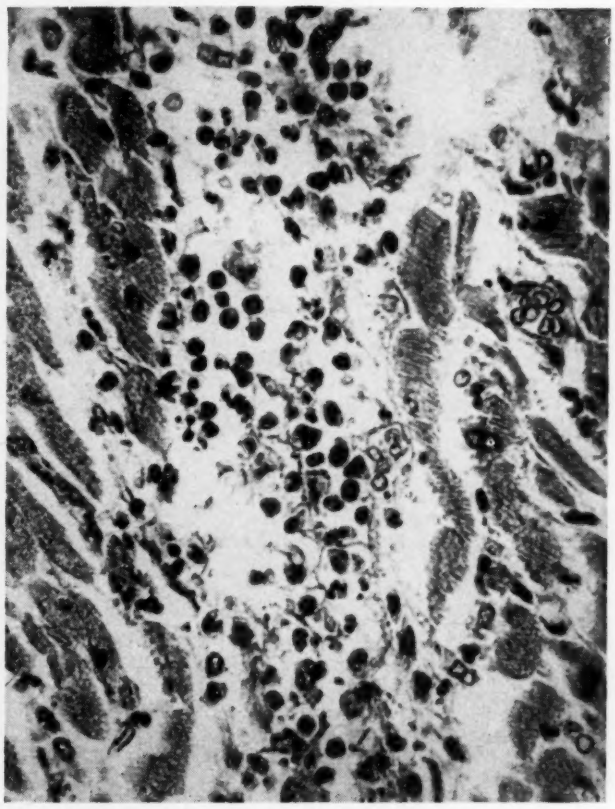

Fig. 2. High power magnification of figure 1 demonstrating the type of infiltrating cells, their pleomorphism, and the presence of polymorphonuclear leukocytes, many of which are eosinophilic in character.

the drug. In this case, however, there was no gross hematuria or loin pain, nor did the patient develop true uremia.

Rather, it appears that the patient's condition fits in with those cases reported from Brooklyn and Baltimore, in which there was generalized tissue reaction with a tubular nephrosis and multiple miliary necrotic foci in many of the organs. This reaction may be primarily toxic, but is more probably based upon an acquired tissue sensitivity. Many of these cases showed effusion into the body cavities. The low plasma protein in this case is difficult to explain. The record does not contain enough data to indicate whether it is connected with a nephrotic syndrome or due to liver damage.

Pathological Discussion

DR. P. KIMMELSTIEL: The pertinent findings at autopsy were marked generalized anasarca, particularly of the face and eyelids. There was also ascites (approximately one liter of fluid) and hydrothorax. The *heart* showed several spotted areas of fibrinous pericarditis and the mottled appearance of a flabby myocardium. Histologically, there was diffuse and severe interstitial myocarditis, chiefly characterized by eosinophils, lymphocytes, plasma cells and a variety of histiocytes. The *lungs* grossly were rather edematous. Microscopically they showed moderately marked interstitial pneumonia; the cells infiltrating the interlobular and interalveolar septa were of the same type as those found in the myocardium. The *kidneys* weighed more than 400 Gm. each. They were swollen and extremely moist. Histologic sections showed extreme interstitial nephritis, with cells of the same type as those found in the heart and lungs densely infiltrating the interstices of the cortex and the corticomedullary junction. The glomerular and vascular apparatus was intact. The tubules, particularly the first convoluted tubules, showed some degenerative changes, including vacuolization, partial disintegration, and occasional necroses; but on the whole the regressive changes were comparatively mild. Most of the nuclei were well preserved. Frozen sections were not made prior to fixation. Therefore, no statement can be made in regard to the presence or absence of sulfonamide crystals. Acute tubular dilatation

Fig. 3. Interstitial nephritis, low power field, showing very slight tubular dilatation and severe inflammatory infiltration.

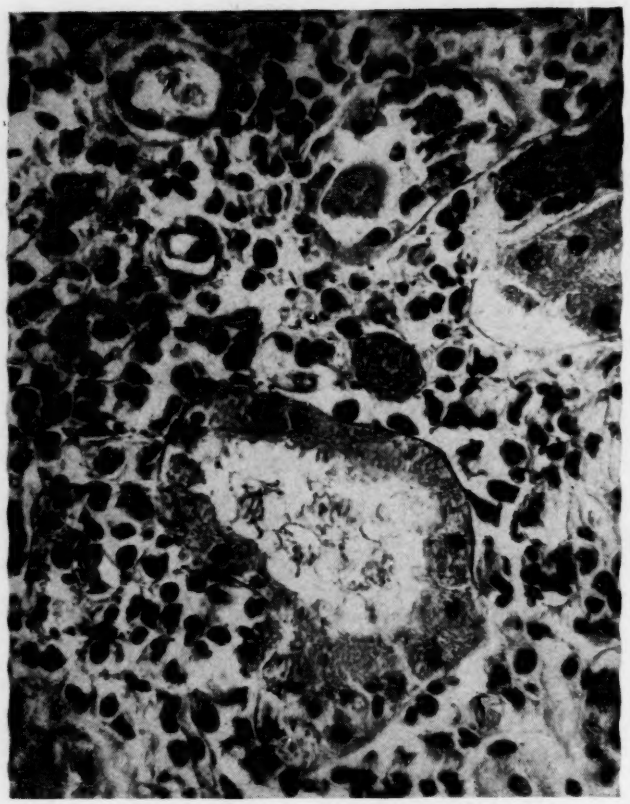

Fig. 4. High power magnification of figure 3.

was negligible; glomerular spaces were occasionally dilated. The *liver* was greatly enlarged, weighing 3300 Gm., and had rounded margins. The outstanding histologic features were severe and extensive dissociation of liver cell cords and fine basophilic granulation of liver cells. No interstitial hepatitis of serous or cellular type was demonstrable.

Interstitial inflammatory infiltration of the type seen in the heart, lungs and kidneys was also found in the pancreas, periadrenal fat tissue, and testes. Several small mucosal ulcers were also noted in the cecum. Grossly and histologically they were nonspecific in appearance.

In *summary*, therefore, it can be stated that the outstanding changes were those of a severe diffuse interstitial inflammatory infiltration of many parenchymatous organs, most prominent in the heart and kidneys, and associated with diffuse degenerative changes in liver parenchyma.

The most outstanding clinical sign, the urinary suppression, is frequently observed in cases of acute hematogenous interstitial nephritis[1]. As a rule the nonprotein nitrogen in such cases jumps rather rapidly to high values and the patient dies in uremia. There is no explanation as to why this sequence of events did not take place in the case under discussion. Furthermore, though moderate albuminuria is often found in cases of interstitial nephritis, it is usually not associated with generalized edema and lowered plasma protein as was the case in this patient. These findings may be explained on the basis of advanced degenerative liver changes. The absence of elevation of blood pressure is rather characteristic of interstitial nephritis which does not involve the glomerular and vascular systems of the kidney. The pericarditis, in our case, was not uremic in nature, but apparently merely an extension of the diffuse interstitial myocarditis.

From the evidence presented, it is safe to conclude that the interstitial inflammation of various parenchymatous organs and the degenerative liver changes were related to the administration of a sulfonamide. There is no reason to assume that the local acute gonorrhea had resulted in systemic involvement of all organs. On the one hand, gonorrheal septicemia could be excluded; on the other hand, the changes described are known

1. Kimmelstiel, Paul: Acute Hematogenous Interstitial Nephritis, Am. J. Path. 14:737-761 (Nov.) 1938.

to occur as a result of sulfonamide administration, even in cases without demonstrable acute infections. Two theories have been advanced as to the cause of urinary suppression: (1) Actual blockage of pelves and ureters by sulfonamide crystals (intrarenal accumulation of sulfonamide crystals is also theoretically assumed to result in obstruction of urinary outflow); (2) so-called "toxic" tubular changes in the kidney. In my opinion, such renal damage can readily be explained on the basis of hyperergic reaction to the drug. Interstitial nephritis with urinary suppression has repeatedly been accurately described in the literature. It has not, however, been specifically termed "interstitial nephritis", but rather has been vaguely referred to as toxic damage resulting from a drug.

In our case, the interstitial nephritis was associated with inflammation of other organs, particularly the heart. Interstitial myocarditis has recently been described as a rather frequent complication of sulfonamide administration[2], and because of its eosinophilic nature, has been ascribed to allergy.

I believe that our case bears the characteristics of allergic reaction to a sulfonamide drug: fever, rash, prostration, leukocytosis, interstitial nephritis, and myocarditis. The unusual features are: (1) severe liver damage with a fall in plasma protein and resultant generalized edema, and (2) the absence of an elevated nonprotein nitrogen and creatinine in the blood, in spite of anuria.

General Discussion

DR. W. E. DANIEL: There are three complications of sulfonamide therapy which involve the urinary tract.

First: The obstruction of the renal tubules by the products of hemolysis in cases of acute hemolytic anemia. This complication may follow acute hemolytic anemia from any other cause, and fortunately is very rare.

Second: Diffuse parenchymatous changes in the kidneys with degenerative tubular damage, which Dr. Kimmelstiel has properly classified as an acute interstitial nephritis. There may also be submucosal hemorrhages along the course of the urinary tract accompanying this condition. I have seen one such case in which one ureter was completely blocked by a large submucosal hemorrhage.

2. French, A. J. and Weller, C. V.: Interstitial Myocarditis Following Clinical and Experimental Use of Sulfonamide Drugs, Am. J. Path. 18:109-121 (Jan.) 1942.

The development of acute interstitial nephritis during sulfonamide therapy presupposes a sensitivity to the particular drug employed and is preceded by the appearance of fever and a drug rash.

Third: Blockage of renal tubules, pelves and ureters by crystals of the drug. This condition does not presuppose a sensitivity to the drug but is due either to large dosage or to limited fluids, or to a combination of the two. It may occur during sulfathiazole, sulfapyridine, and sulfadiazine administration, but has not occurred following sulfanilamide therapy, probably because sulfanilamide is much more soluble than the other three drugs. This complication can be avoided by maintaining an adequate fluid intake and by using smaller doses of the drug. It is unfortunate that the first advocates of sulfonamide therapy thought that high concentrations of the drug in the blood and urine were necessary. They even went so far as to limit the fluid intake in order to assure a higher concentration in the urine. Fortunately this was in the early days, and the drug used was sulfanilamide, which is comparatively soluble and is not likely to crystallize. If fluids are reduced during the administration of sulfathiazole, sulfapyridine, or sulfadiazine, trouble is invited. In urological practice, we never use more than 2 Gm. daily and have found this dosage just as effective as the larger doses used formerly.

In closing, I would like to put in another plea for adequate fluid intake and smaller dosage. These drugs are capable of performing miracles, but are also loaded with dangers for the careless user.

DR. M. T. GILMOUR: It is becoming increasingly clear that renal complications constitute one of the most important dangers in the use of the sulfonamide drugs. The mechanisms by which oliguria and anuria occur have already been enumerated by Dr. Daniel.

It seems to me that this case is of unusual interest in this connection and that Dr. Kimmelstiel's observations regarding it are of fundamental importance. Although the lesions pointed out by Dr. Kimmelstiel have been described by others, nowhere in the literature do I find that they have been recognized as constituting an acute interstitial nephritis. Their proper classification as such may serve as the key to the solution of this entire problem.

In this connection we are led directly to the subject of sensitivity to the sulfonamide drugs. Experimental evidence shows that animals may be sensitized to certain azoprotein linkages of these drugs but not to the pure drug itself. Clinical experiments reported by one group of workers indicate that about one-third of the patients receiving a sulfonamide drug may be expected to develop some type of sensitivity to it. It has been shown that this may develop within nine days or even less, and that in some cases at least, it may last as long as two years. Some authors have reported test cases in which sensitivity to the drug has developed and in which a recurrence of fever and at times of rash and of generalized symptoms suggesting grippe occur each time the drug is again administered. In these cases, the size of the dose does not seem to be important; amounts as little as 1/10 Gm. often have the same effect as larger doses. Anuria has been reported from a total dose as small as 12 Gm., and death from as little as 17 Gm. The sensitivity does not seem to be entirely specific for each particular drug. At times a patient sensitive to one of the sulfonamides may be able to take another without difficulty, but in such cases a special caution must be exercised.

The implications of these facts are of great importance. In giving the drug, we must exercise the same care and judgment as are required in the administration of serum. Before prescribing any of these drugs we must always consider three possibilities: There is the unpredictable chance that an idiosyncrasy or hypersensitivity to the drug may exist and may result in a severe hemolytic anemia within twenty-four hours. Then there is also the possibility that the patient, through previous use of the drug, may have acquired a sensitivity to it. As yet it is not possible to detect these patients, as it is to detect patients who are sensitive to serum, and this danger is thus particularly difficult to avoid. And finally, there is the possibility that the patient, by his use of the drug, may become sensitized so that in the future its use in a more serious illness may be dangerous.

It thus becomes necessary to determine, if possible, in every instance whether the condition from which the patient is suffering is sufficiently serious and sufficiently likely to be benefited by the drug to warrant the risks involved in its use. The indiscriminate use of these valuable but potentially dangerous drugs for upper respiratory infections and other minor conditions, in which they are probably useless anyway, cannot be too strongly condemned, particularly when the drug is given at home without close clinical or laboratory observation.

During the administration of the drug in the hospital, diligent care must be exerted to detect at the earliest possible moment any toxic effect that may arise. Hospital routine should include the keeping of a simple, standardized fluid balance sheet on each patient receiving a sulfonamide drug. This should be started automatically without the necessity of a special order. In addition to the frequent examinations of the urine and blood which are required, it is important to observe the skin and eyes closely each day to note the earliest appearance of any rash or of anything suggesting a conjunctivitis. Obviously, any pain in the loins or back must be carefully evaluated. The patient must also be protected against harm which might come from the occasional mental disturbances which occur. The appearance of fever or of chills and fever in a patient taking one of the sulfonamide drugs must always suggest the possibility of drug fever. Similarly, continuation of fever which cannot be explained on any clinical basis must also suggest this possibility. If drug fever is suspected the drug must be immediately discontinued. This decision is often a difficult one to make.

Patients who have received any one of the sulfonamides should be informed of that fact before they leave the hospital so that they may be able to give a correct answer to inquiries on this score in the future. The diagnosis sheet or the chart of each of these patients should likewise state that a sulfonamide drug has been administered, and if any evidence of toxicity or sensitivity was observed, this should be especially noted. These facts should be conspicuously placed and not buried on the order sheets or in the progress or nursing notes.

Finally, let me emphasize once more that these drugs are not an unmixed blessing. As valuable as they are, they may also be dangerous, and their action is not as yet entirely understood. Our enthusiasm for the sulfonamides must be mixed with a healthy leaven of caution and respect so that we may use

them with discretion and good judgment and not simply as a cloak for ignorance or helplessness in the face of a difficult situation.

CLINICO-PATHOLOGICAL CONFERENCE

Duke Hospital

J. LAMAR CALLAWAY, M. D.
and
DOUGLAS SPRUNT, M. D.

DR. CALLAWAY: This patient was a 36 year old colored woman who was admitted complaining of right upper quadrant pain and abdominal distention of ten days' duration.

The *family* and *marital* histories were noncontributory.

The *past history* showed that the patient had always been obese but otherwise had been in good health. She had had intermittent frontal headaches for the past several years, and because of this she was fitted with glasses six months ago. About one year ago she had some dependent ankle edema. Ten weeks prior to admission the patient consulted her physician because of weakness, and at that time was found to have a positive Wassermann reaction; treatment was begun with weekly intravenous injections of neoarsphenamine. During the past year she had drunk up to one quart of gin per day and smoked about twenty cigarettes daily.

Her *present illness* began ten days ago, after her seventh intravenous injection of neoarsphenamine, when she began to have right upper quadrant pain with abdominal distention. There was associated nausea and vomiting, but the vomitus contained only the food previously eaten and at no time showed any blood or coffee-ground material. She felt feverish and broke out with a generalized eruption involving the extremities and trunk. She noted that her urine was becoming darker and that her stools were becoming lighter in color, and about a week before admission her eyes became quite yellow. There had also been some moderate diarrhea, consisting of three to four watery stools each day.

On *admission* the patient had a temperature of 39.5 C., pulse 120, respirations 20, blood pressure 150 systolic, 100 diastolic. She was an obese, perspiring, pleasant 36 year old Negro woman lying flat in bed, restless, and complaining of being hungry. The skin was warm and moist but there was no significant eruption at the time. Her sclerae were icteric. The pupils were round, regular and equal, and reacted to light and on accommodation. The fundi were normal. The teeth were dirty. The tongue was coated and red. The chest was symmetrical; the percussion note was somewhat dulled throughout but the breath sounds were normal. The heart was enlarged to the left; the rate was 120, the rhythm was regular, and there were no murmurs. The abdomen was very obese and there was marked tenderness in the right upper quadrant. The liver was enlarged 6 cm. below the right costal margin and was very tender. No free fluid could be demonstrated in the abdomen. The neurological examination was negative.

Accessory clinical findings revealed a hemoglobin of 87 per cent, 4,420,000 red blood cells, a color index of 1.08, a hematocrit of 40.5 volumes per cent, and a mean corpuscular volume of 91 cubic micra. The white blood cell count was 7,250, with a differential showing 72 per cent polymorphonuclear segmented forms, 9 per cent stabs, 5 per cent juveniles, 2 per cent large lymphocytes, 8 per cent small lymphocytes, and 6 per cent monocytes. The Wassermann, Kahn, and Kline reactions were strongly positive. Blood chemistry studies showed a nonprotein nitrogen of 32 mg. per 100 cc., with a direct van den Bergh revealing a bilirubin of 7.4 mg. per 100 cc. The total serum proteins were 5.5 Gm. per cent, with an albumin-globulin ratio of 0.9. The bromsulfalein test showed 40 per cent retention. The blood sugar was 133 mg. per 100 cc. A galactose tolerance test disclosed 7.4 Gm. of galactose excreted. A flat plate of the abdomen was negative except for the fact that the liver was considerably enlarged. Serum phosphorus was 4.1 mg. per 100 cc., with the phosphatase showing 16.4 Bodansky units. The urine showed a specific gravity which varied between 1.010 and 1.022. The sugar and albumin tests were negative.

Course in Hospital: The patient was placed on a high carbohydrate, low fat diet supplemented by thiamin chloride, nicotinic acid and cevitamic acid. She was given intravenously 750 cc. of 10 per cent dextrose daily. Her condition grew progressively worse. She continued to complain of right

upper quadrant pain and became more jaundiced. The temperature, which on admission had been normal, rose to 39.3 C. on the sixth day, and she expired after being delirious, restless, and noisy for the previous twenty-four hours. The serum bilirubin two days prior to death was 23.2 mg. per 100 cc.

Discussion

The differential diagnosis in this patient is interesting in that there are at least eight fairly good possibilities to be considered, as follows:

1. Acute cholecystitis with or without cholelithiasis
2. Catarrhal jaundice
3. Alcoholic cirrhosis
4. Acute syphilitic hepatitis
5. Late gummatous hepatitis
6. Jarisch-Herxheimer reaction
7. Malignancy
8. Arsenical hepatitis

Acute cholecystitis at first glance seems to be substantiated by the right upper quadrant pain and tenderness at the time of examination. The direct van den Bergh of 7.4 mg. per 100 cc. also is confirmatory. The pain, however, did not radiate and was not the type of colicky pain usually associated with cholecystitis. A simple catarrhal jaundice which had appeared incidental to syphilis and to antisyphilitic treatment is a good possibility, and is frequently seen in patients undergoing antisyphilitic therapy. Patients with catarrhal jaundice, however, are not as a rule as ill as this patient was and tend to recover in a short time.

The history of the ingestion of large quantities of alcohol suggests the possibility of alcoholic cirrhosis, and, although the onset was very rapid and there was considerable pain, this possibility has to be borne in mind. Acute syphilitic hepatitis must be considered, but there is no indication that she had an early syphilitic infection. Therefore, I do not think it likely that this represents parenchymatous involvement by the Spirochaeta pallida. Gummatous syphilitic hepatitis is a rather rare disease and seems a remote possibility.

The onset of her present illness after the seventh intravenous injection of neoarsphenamine tends to rule out the Jarisch-Herxheimer reaction, although this edematous reaction following antisyphilitic therapy must be considered. As a rule, the Jarisch-Herxheimer reaction follows the first or second treatment. Malignancy in or around the common duct might produce signs and symptoms not unlike those presented by the patient.

Arsenical hepatitis seems to me to be the most probable etiologic factor since, in addition to right upper quadrant pain, enlarged liver, and jaundice with the associated clinical findings, she also developed a cutaneous eruption which probably was a reaction to the arsenical. In view of the rapid downhill course, despite all therapy, I think that arsenical hepatitis certainly outweighs the other possibilities, and I believe that this patient's liver will show rather extensive necrosis throughout, such as is seen in acute yellow atrophy.

Dr. Callaway's Diagnosis

Acute yellow atrophy of the liver, due to arsenical hepatitis

DR. FREDERIC M. HANES: Dr. Callaway's clear analysis and conclusions have doubtless convinced all of us that this is an instance of acute yellow atrophy, due to the poisoning of the liver cells by arsenic. Such a diagnosis is rather shocking, as are all therapeutic accidents, but it should impress us anew with the serious dangers attending the use of arsenical compounds in therapy. The physician using arsenicals should never forget that he is employing one of the deadliest of all poisons, and he should be alert to the least evidence of intolerance or over-dosage. Arsenical dermatitis is bad enough, but hepatitis and encephalitis are often rapidly fatal.

Anatomical Discussion

DR. SPRUNT: At autopsy the skin was jaundiced and numerous petechial hemorrhages were seen. The heart was enlarged, weighing 750 Gm. There was insufficiency of the aortic valve, due to syphilis, which also involved the aorta and partially occluded the coronary arteries. There were a number of petechial hemorrhages on both epicardium and endocardium. The lungs were edematous and there was some chronic passive congestion. A few focal areas of broncho-pneumonia were found and also some small hemorrhages on the pleura.

The liver weighed 1200 Gm. and was intensely jaundiced. Extensive necrosis was

seen throughout. The only intact cells were in the periportal region. In spite of the extensive necrosis there was no cellular infiltration except for a few macrophages in the periportal region.

The kidneys each weighed about 350 Gm. They were markedly swollen. Microscopically they showed a small amount of arteriolar sclerosis, and some damage to the glomeruli. The blood vessels and glomeruli contained some visible fat, but fat was most strikingly present in the convoluted tubules. There was also a large amount of bile in the tubules.

The other organs, including the brain, showed little except chronic passive congestion.

Death in this case was obviously due to the necrosis of the liver (acute yellow atrophy). Although we cannot prove it, we believe the cause to have been the arsenical therapy, particularly since the arsenic was continued after the onset of symptoms. The damage to the liver resulted in the accumulation of bile in the circulation, with excretion by the kidney and marked damage to the kidney.

In addition to these findings there was some vascular damage to the kidney with resultant cardiac hypertrophy, and also a syphilitic involvement of the aortic valve and the coronary orifices which led to cardiac failure and chronic passive congestion of the viscera.

Anatomical Diagnosis

Syphilitic aortitis with involvement of the aortic valve and partial occlusion of the coronary orifices

Acute yellow atrophy of the liver
Jaundice
Petechial hemorrhages
Bile nephrosis
Mild arteriolarsclerotic nephritis
Cardiac hypertrophy and dilatation
Generalized arteriosclerosis
Chronic passive congestion of the viscera
Pulmonary edema
Terminal broncho-pneumonia.

There can be no such thing as chronic pulmonary tuberculosis without a first infection. However, it is not usually the first infection that is important—what matters most is the subsequent superinfections and reinfections which should be guarded against in the infected group.—David Zachs, M.D., Jour. of School Health, June, 1942.

MEDICOLEGAL ABSTRACT

J. F. Owen, M. D., LL. B.
Raleigh

Abortion: Statutory provisions are made for two separate offenses. Proof must conform to the allegations.

This is a criminal case in which a doctor was charged with performing an operation upon a woman "quick with child", with intent thereby to destroy the child.

Upon the trial in Superior Court the evidence of the State tended to show that the pregnant girl, 15 years of age, became pregnant in January, 1942, and that the operation was performed on March 28, 1942—after a period much shorter than half the term of pregnancy, at which time there is supposed to be quickening of the child. The operation which brought about the abortion was not necessary to preserve the life of the woman upon whom the operation was performed. It was also brought out in the testimony that this operation was performed by the physician for a stipulated fee.

The defendant in the case plead not guilty, offering evidence tending to show an alibi, upon which he relied as a defense. When the State rested its case the defendant moved to dismiss the case by a judgment as of nonsuit. The motion was denied, and the defendant excepted; again at the close of all the evidence the defendant renewed his motion for judgment as of nonsuit. Motion was denied, and again he excepted.

The verdict of the jury in this particular case was that of guilty, and the defendant was sentenced to serve in the State's prison for a period of not less than two and one-half or more than five years, and assigned to such labor as provided by law. The defendant appealed to the Supreme Court, and assigned error.

When this case came on to be considered by the Supreme Court, the Justice writing the opinion called attention to the fact that in this state there are two separate and distinct statutes pertaining to abortion, one of which makes it unlawful to administer drugs to or perform an operation upon a woman "either pregnant or quick with child with intent thereby to destroy the child." The other statutory provision with reference to abortion makes it unlawful to administer drugs to or to perform an operation upon "a pregnant woman with intent thereby to procure the miscarriage of such woman, or to injure or destroy such woman." Greater punishment is prescribed for a violation of the provisions of the first mentioned statute than for a violation of the latter. Manifestly, it was the intention of the Legislature to declare two separate offenses.

The question then arose as to how far pregnancy should be advanced before the child is considered capable of being destroyed. While, for many purposes, a child in **ventra sa mere** is supposed in law to be born, Blackstone states that "life begins in contemplation of law as soon as an infant is able to stir in the mother's womb."

The evidence tended to show that pregnancy in this particular instance had not advanced to the extent that there was quickening of the child, proof of which was required by the statute under which the bill of indictment was drawn. The proof, according to the opinion of the Justice, did not conform to the allegations. For that reason the defendant's motion for judgment as of nonsuit should have been granted. Therefore the judgment of the Superior Court was reversed.

Although there are statutory provisions in North Carolina for two separate offenses, as far as abortion is concerned, depending upon the progress of gestation, there is very little consolation for one engaged in this type of surgery, inasmuch as both offenses are felonies. Upon conviction there is a rather severe sentence invoked, consisting of terms in the State's prison and of course the probability that the convicted person would have his license revoked. (Vol. 222, Page 537. Decision rendered January, 1943.)

Schedule For Twenty War Sessions Announced by American College Of Surgeons

New developments in military and civilian medical and hospital service will be brought to members of the medical profession at large, and hospital representatives, through a series of twenty War Sessions, beginning March 1, to be held throughout the United States under the sponsorship of the American College of Surgeons with the cooperation of other medical organizations and of the Federal medical services.

Each War Session will consist of an all-day program, lasting from 9:00 o'clock A. M. to 10:00 P. M., including luncheon and dinner conferences. There will be eight meetings in each session, four of which will be for the entire assembly, and the remainder divided into two meetings each for physicians and for hospital representatives. Subjects will be similar in the different places but some of the speakers will be changed in the different states and service commands. Nationally known representatives of the United States Army, the United States Navy, the United States Office of Civilian Defense, the United States Procurement and Assignment Service, and the United States Public Health Service, will address the meetings and will lead discussions, in addition to participation by prominent leaders in civilian medical practice and hospital service.

Topics to be discussed relating to military medicine will include care of the ill and injured in combat zones and after evacuation. The newer types of injuries encountered in this war, such as crush and blast injuries, will be especially considered, together with prevention and treatment of infections, and treatment of burns, shock, and injuries of specific parts of the body. Anesthesia, plastic surgery, and the psychoneuroses of war, will be some of the other topics. Problems of civilian medical care in wartime which will be discussed will include the responsibilities of individual doctors and hospitals; personnel problems of hospitals; organization of emergency medical services; maintaining adequate supplies, furnishings, and equipment; maintenance of high standards of medical and nursing education, and of hospital service in general; hospital public relations; and administrative adjustments in professional staffs of hospitals. The opening meeting of each session will be devoted to discussion of "Medical and Surgical Aspects of Chemical Warfare," led by a representative of the United States Office of Civilian Defense, and the closing meeting will be a panel discussion on problems in wartime civilian medical practice to be led by representatives of the United States Public Health Service, the American College of Physicians, the American Medical Association, medical services in industry, and the American College of Surgeons. Some of the topics for consideration at this meeting will be endemic and epidemic diseases, including tropical diseases; medical services in industry; medical and surgical practice; and supplementary postgraduate education for medical officers and civilian doctors.

The War Sessions for North and South Carolina will be held in Charlotte at the Charlotte Hotel, on Monday, March 22.

The American College of Surgeons cancelled its 1942 national meeting and is holding in abeyance plans for a Clinical Congress in 1943, in the meantime offering the regional meeting plan provided by the War Sessions to save the time of the doctors and other personnel, and to minimize transportation difficulties, without sacrificing unduly during wartime the educational and stimulative benefits of medical assemblies.

Medical Meetings During the War

Mr. Stephen McDonough, Washington, in a letter to Mr. C. P. Loranz, Secretary-Manager, Southern Medical Association, just prior to the Richmond meeting of the Association in November, 1942, said:

> "Last Friday I rode over from the Munitions Building to the new Pentagon Building with Dr. Vannevar Bush, Director of Scientific Research and Development, and I mentioned the holding of scientific meetings in wartime. He said: 'Physics meetings? No. Chemical Society meetings? No. Medical meetings? By all means they should be continued with even greater emphasis than before. We must preserve and disseminate advances in medical knowledge as never before.' If you need any better opinion than that I don't know where to find it."

Our information is that Dr. Vannevar Bush is President of the Carnegie Institution of Washington, a research organization, was formerly President of the Massachusetts Institute of Technology, and is one of the greatest living electrical engineers. He built the differential analyzer, a mechanism that solves the most intricate differential equations, and the network analyzer to solve power transmission problems, two of his most notable scientific contributions in his field of work.

Mr. Stephen McDonough, prior to late summer of 1942, was for a number of years Science Writer for the Associated Press. He covered the annual meetings of the Southern Medical Association for the Associated Press for some six years prior to and including the St. Louis meeting in November, 1941. Since late summer of 1942 he has been serving his country as a Captain, U. S. Army, Office of Chief of Ordnance, Washington.

Announcement From American Red Cross Headquarters

Dr. John F. Busch has been appointed Director of Medical and Health Service for the Eastern Area of the American Red Cross, with headquarters in Alexandria, Virginia. North Carolina is included in this area. Dr. Busch has been associated with the Division of Tuberculosis Control of the Georgia State Department of Public Health since 1937. Before that time he was engaged in general practice in Spartanburg, South Carolina.

BULLETIN BOARD

News Notes From the State Board Of Health

Our infant mortality rate in North Carolina last year was the lowest on record. In 1941 there were 5,073 deaths among infants under a year old, with a rate of 59.4 per one thousand live births. In 1942 the total was only 4,281, in spite of the marked increase in the number of births, and the infant mortality rate dropped to 47.5 for the entire year, throughout which there was a sustained downward trend.

Not only was the infant mortality rate in North Carolina last year the lowest on record, but the same was true of the general death rate, which was 8.1. There also was a sharp decline in the total number of deaths, which was only 29,613, as compared with 32,154, during the preceding year.

Note the two extremes that marked North Carolina's vital statistics for 1942—the greatest number of births on record, and the lowest death rate. It is interesting to note that there were 60,443 more births than deaths recorded.

During the year there were only 21 deaths from typhoid fever, a disease which, during the War With Spain in 1898, claimed more victims than did Spanish bullets, while the total number of deaths from influenza, which wrought such havoc during the First World War, was only 296, as compared with 902 in 1941.

There was also an appreciable reduction in the number of deaths from tuberculosis in all forms, the 1942 total having been only 1,578 for the entire State, as compared with 1,769 in 1941, the rate having fallen in a single year from 48.8 to 43 per 100,000 persons. There was a sustained decline in the number of pneumonia deaths, which last year totaled only 1,677, as compared with 1,896 in 1941, bringing the rate down from 52.3 to 45.8 per 100,000 inhabitants.

There was a sharp decline in deaths from diarrhea and enteritis among children under two years of age, the 1942 total having been only 464, as compared with 692 the preceding year, bringing the rate from 19.1 to 12.6 in twelve months.

Appreciable decreases were recorded in the number of both suicides and homicides, while the number of deaths from what are termed preventable accidents was only 1,513, as compared with 1,862 in 1941. This total was materially affected by the downward trend in traffic deaths, which has been very noticeable since rationing began and since the speed limit has been reduced.

Deaths attributable to air transportation accidents, however, increased from 92 to 104; from accidental burns, from 213 to 220; and from traumatism by firearms, from 74 to 91, while the number of persons accidentally drowned increased from 143 to 182.

* * * *

During the first World War there were 157,146 more new cases of syphilis and gonorrhea among the soldiers, sailors and marines of the United States than there were wounds in battle itself. Total absences from duty, due to venereal diseases, kept the equivalent of 20,600 men out of the fighting for a whole year—men trained for their country's service, men upon whom their country counted for its defense. Think of such loss in terms of today's hard-held battlefronts. Twenty thousand men would mean five huge aircraft carriers and nine destroyers. Think of what those carriers would mean in the battle of the Pacific, what vital protection these destroyers would give our ships in the battle of the Atlantic.

Doctor Eliot Ness, Director of Social Protection, Office of Defense Health and Welfare services, is authority for the statement—made at a conference in this State recently—that out of the first two million men examined for military service in the present war, 100,000 had to be deferred because of syphilis. The Army and the Navy, he continued, felt that to get the best results, there had to be cooperation among the civilian communities, as one-third of the venereal diseases could be traced to towns and cities sometimes 200 miles from camps. In many sections, he declared, segregated, or red light, districts were found to exist, often with the approval of the police officials. He declared that segregation is the worst kind of control; that it is medically, as well as morally, unsound. Where segregated districts have been closed, Dr. Ness pointed out, venereal disease rates have decreased and conditions in communities where these districts formerly existed have become more orderly.

* * * *

Dr. Donnell B. Cobb, President of the Medical Society of the State of North Carolina, has issued the following statement with regard to the proposed setting up of a central supervising board for hospitals for the mentally sick:

"Some months ago the committee appointed by Governor Broughton to investigate the Morganton State Hospital made its report. It was found that North Carolina, who prides herself on many things, was forty-fifth among the forty-eight states in the amount it spends for the care and treatment of the helpless insane. Certainly this is something of which we can not be proud.

"Acting upon the recommendations of the Governor's investigating committee, a bill has been introduced in the legislature to set up a North Carolina hospital board of control to supervise the Morganton, Raleigh and Goldsboro Hospitals and the Caswell Training School in Kinston.

"The physicians of North Carolina endorsed the recommendations of this investigating committee and they are in accord with the idea of setting up a central state supervising board. Success of such a central governing board depends entirely upon how it is set up and who constitutes its members.

"The creation of this board will, in all probability, determine the administration of mental institutions and the care of mental patients in North Carolina for the next quarter of a century. During recent years a marked change has occurred in the general attitude toward mental sickness. In quite a few states laws have been drafted and boards have been set up in accord with the viewpoint of modern psychiatry, that mental illness is a medical problem and is as susceptible to prevention, treatment and cure as human sickness in general.

"The recommendations of the Morganton Investigating Committee and the creation of an efficient central board can not accomplish all that is needed for the incarcerated and helpless mentally sick. There must also be a reawakening of official and individual state wide interest in these most unfortunate individuals. Every effort should be made to prevent mental sickness and, too, to return as many of the mentally sick as possible to a useful place in Society.

"In the betterment of existing conditions the Medical Profession is intensely interested and it desires to work with the Governor in this effort to make the care of mental patients something of which the State of North Carolina can be very proud."

MATERNITY SUMMER SESSION
UNIVERSITY OF NORTH CAROLINA

For preparation in maternity service, graduate nurses are invited to attend the Summer Session at the University of North Carolina. "The Public Health Nurse in a Maternal Health Program" will be offered to Public Health Nurses during the first Summer Session at the University of North Carolina at Chapel Hill, June 7 to 27, 1943. The Department of Public Health Nursing, through the School of Public Health, will direct the activities. Miss Louise Zetzsche, Supervisor of Maternal and Infant Welfare, Denver Visiting Nurse Association, Denver, Colorado, will be guest instructor. Four and one-half quarter hours of credit will be awarded upon completion of the course. For further information, write to Miss Margaret Blee, Assistant Professor of Public Health Nursing, Department of Public Health Nursing, School of Public Health, University of North Carolina, Chapel Hill, North Carolina.

NEWS NOTES FROM THE NORTH CAROLINA
TUBERCULOSIS ASSOCIATION

Annual Meeting Called Off

At a meeting at the Carolina Hotel in Raleigh on the evening of January 21, 1943, the Executive Committee of the North Carolina Tuberculosis Association weighed carefully the question of holding an Annual Meeting this spring. Because of the expressed desire of the Office of Defense Transportation that travel be limited to the lowest practicable minimum, it was decided to dispense with the usual Annual Meeting and arrange for the business of the Association and problems of control of tuberculosis to be handled at a meeting of the State Board of Directors, to be held probably some time in May. This is in line with the action of the National Tuberculosis Association, which has cancelled its Annual Meeting for the same reason.

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"The Eastern North Carolina Sanatorium opened its doors to patients on January 15, 1943, as the transfer of seventy patients from the northeastern counties, who were receiving treatment at the North Carolina Sanatorium, began. Forty-three patients from the Main Division of the North Carolina Sanatorium and twenty-seven from the Negro Division were moved during the first few days of operation. Dr. H. F. Easom, Associate Superintendent and Medical Director of the new hospital, said that more than a hundred patients are eligible to be moved from the North Carolina Sanatorium but that transportation difficulties might cause a delay in the transfer. After the transfers are made, the hospital will receive two or three patients a day until the remaining beds are filled, Dr. Easom said.

"The State's new sanatorium for the treatment of tuberculosis consists of separate units for white and negro patients, with a present capacity of 110 beds in each unit. The buildings were completed last fall and dedicated on September 23 at ceremonies at which Governor J. Melville Broughton was the main speaker. The actual operation was delayed on account of difficulties in securing some of the equipment.

"No special ceremonies marked the opening of the hospital on January 15. Dr. P. P. McCain, Superintendent of North Carolina Sanatoria, was in Wilson to supervise personally the transfer of the patients and the opening of the hospital."—The Sanatorium Sun.

The most important advance in tuberculosis control in the State during the past two years, according to Dr. P. P. McCain, was the building of the Eastern North Carolina Sanatorium, with 110 beds for white and 110 beds for negro patients. In addition five counties, Wilson, Anson, Alamance, Wayne and Martin, have opened sanatoria and the Wake County Sanatorium has added 30 beds. These local units have a total of 64 beds for white and 80 beds for negro patients, which together with the Eastern Sanatorium makes 364 new beds added in two years. There are now 23 counties which have their own sanatoria with a combined bed capacity of 521 for white and 417 for negro patients.

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Officials of the Red Cross Sanatorium in Wilmington report that disturbances from airplanes will soon force the closing of the hospital which, since the government has established so many war activities in Wilmington, is now surrounded by an air field. Attempts to find quarters for patients have so far been unsuccessful because of the crowded living conditions in the area. Dr. J. C. Wessell, Medical Director of the sanatorium, has expressed the hope that money can be secured for building a new hospital as soon as materials are available.

* * * *

Word has just been received that Mr. Page, formerly with the North Carolina Tuberculosis Association, has successfully completed training in Officer's Candidate School at Fort Benning, Georgia, and has been commissioned as a lieutenant. He is now located at Camp Croft, Spartanburg, S. C.

* * * *

Dr. H. A. Pattison's new volume, **Rehabilitation of the Tuberculous**, is now ready for immediate mailing. Based on his quarter century of first hand experience and visits to foreign rehabilitation projects, the book covers many aspects of a most complicated problem, including psychological factors, placement and compensation. Compact, yet comprehensive, **Rehabilitation of the Tuberculous** will amply repay the most careful reading by every health worker. The price of the book is $2.00.

NEWS NOTES FROM THE BOWMAN GRAY SCHOOL OF MEDICINE OF WAKE FOREST COLLEGE

Dr. Tinsley Harrison, Professor of Medicine, spoke at the Founder's Day exercise of the Duke Chapter of the Phi Chi Medical Fraternity on February 24. Dr. Harrison held a clinic at 11 a. m. on "The Differential Diagnosis of Pain in the Chest", and in the evening spoke on "Cardiac Dyspnea".

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Dr. Wingate M. Johnson, Professor of Clinical Medicine, spoke before the Richmond Academy of Medicine at Richmond, Virginia, on March 9. His subject was "J. Marion Sims: Medical Pioneer".

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Dr. Arthur Grollman, Research Professor of Medicine, gave a talk on "Experimental Studies in Hypertension" before the Duke Medical Society in Durham on March 9.

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A paper by Dr. William Allan and Dr. C. Nash Herndon, of the Department of Medical Genetics, was presented before the regional conference of the American Association on Mental Deficiency, held in Atlanta on March 10. The title of the paper was "Some Examples of the Inheritance of Mental Defect".

News Notes From the University of North Carolina

Dr. William deB. MacNider presented a paper on "The Susceptibility to Injury of Liver and Kidney Epithelium—A Consideration of the Factor of the Age of the Organism" at the meeting of the American Division of the Club for Research on Ageing in New York on February 13. Dr. MacNider is Chairman of the Club.

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Dr. Russell L. Holman, Professor of Pathology, and Dr. D. A. MacPherson, Professor of Bacteriology, will attend the courses on Tropical Medicine at the Army Medical School and Tulane University, respectively, during the months of March and April, which are financed through the generosity of the Markle Foundation.

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Dr. R. T. Shields, formerly of Cheeloo University School of Medicine, China, has joined the Department of Pathology as Acting Associate Professor to replace Dr. Clark E. Brown, now on duty with the Navy Medical Corps.

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The new Naval Infirmary was formally opened on February 8. This building is of fire-proof construction, is splendidly equipped, and has a bed capacity of approximately 100. It is situated to the rear of the present Medical Building and will be available for University needs after the war.

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Dr. W. R. Berryhill attended a meeting of the Council on Medical Education and Hospitals in Chicago on February 15 and 16.

Cabarrus County Medical Society

Dr. James F. O'Neill of the Bowman Gray School of Medicine spoke to the Cabarrus County Medical Society at its meeting on February 16, held at Concord. Dr. O'Neill gave "A Survey of Patients Seen and Treated for Carcinoma of the Lung Over a Fifteen Year Period".

Columbus County Medical Society

Dr. R. B. Whitaker of Whiteville was elected president of the Columbus County Medical Society at its January meeting. Dr. Thurston Formyduval of Whiteville was named vice president, and Dr. W. A. Greene of Whiteville secretary and treasurer. Henceforth the society will meet only four times a year, instead of monthly. The meetings will be held on the second Monday night of each quarter.

Forsyth County Medical Society

The Forsyth County Medical Society held a dinner meeting on February 9 in Winston-Salem. Dr. S. D. Craig, State Chairman of Civilian Defense, and Colonel Dwar, in charge of Civilian Defense Affiliated Base Hospitals, spoke on the organization of affiliated base hospital units for emergency care of civilians. Members of the program committee presented a program on "What Was New in Medicine in 1942". Dr. Tinsley Harrison discussed advances in medicine; Dr. Arthur Grollman, advances in chemotherapy; Dr. W. H. Sprunt, surgery; Dr. Fielding Combs, nose and throat; Dr. Ruth Henley, obstetrics; Dr. James F. O'Neill, the technique of operation for cancer of the stomach; and Dr. R. A. Moore, the Kenny treatment of poliomyelitis.

Haywood County Medical Society

The Haywood County Medical Society held its regular meeting on February 18. Dr. M. B. H. Michal read a paper on "Infant Feeding".

National Health Advisory Council

A National Health Advisory Council was organized in Washington on February 5 to project and carry out a broad program looking to health conservation as one of the most important factors in winning the war. The Council was created by the Chamber of Commerce of the United States to consider national health problems in relation to the war program.

The National Health Advisory Council will serve to channel approved technical health information developed by the country's many scientific associations to business organizations and their members throughout the country, so there may be brought about a better public understanding and appreciation of medical science as a means of safeguarding public health to win the war. It will work through the Chamber of Commerce of the United States as a central organization, which, in turn, will work through its far flung membership of trade associations, chambers of commerce and corporations and firms. The Council's membership starts with thirty of the nation's leading medical and health authorities. This membership will be increased as the work progresses.

American College of Chest Physicians Cancels 1943 Meeting

The following resolution was adopted by the Board of Regents of the American College of Chest Physicians at their Mid Winter Meeting at the Palmer House, Chicago, February 14, 1943.

WHEREAS: The American Medical Association has cancelled its annual meeting for the year nineteen hundred and forty-three; and

WHEREAS: The American College of Chest Physicians has since its inception held its meetings jointly with the annual meetings of the American Medical Association,

BE IT RESOLVED, That the Board of Regents of the American College of Chest Physicians meeting in Executive Session in the City of Chicago on the fourteenth day of February in the year nineteen hundred and forty-three, hereby proposes that the 1943 annual session of the American College of Chest Physicians be cancelled and that the reasons for the cancelling of this meeting are the same as those advanced by the Executive Council of The American Medical Association.

It was recommended by the Board of Regents that wherever feasible, State and District Chapters of the College arrange to meet jointly with their State and District Medical Societies and assist in preparing scientific programs concerning the specialty of diseases of the chest.

Dr. Karl Schaffle, Asheville, is the Regent of the American College of Chest Physicians for the Southeastern States.

Urological Research Prize Not To Be Offered This Year

The $500 Research Prize annually offered by the American Urological Association will not be awarded this year, and plans for the June meeting of the American Urological Association in St. Louis have been cancelled.

American Association on Mental Deficiency

The regional conference of the American Association on Mental Deficiency was held in Atlanta, Georgia, on March 10. Dr. W. T. Parrott of Kinston, Superintendent of the Caswell Training School, is regional chairman and presided at the conference. Mr. E. M. Brown, of the Caswell Training School, is regional secretary.

Announcement From California State Personnel Board

Qualified applicants are desired for two important civil service positions with the California State Department of Institutions. The two examinations to be given are for Assistant Medical Director and Superintendent, Mental Hospital. Because of the importance of these two positions, the tests will be conducted on a nation-wide basis and will be open to both men and women who are qualified.

Resolutions From the Pinellas County Medical Society, Inc. (Florida)

The Pinellas County Medical Society, in executive session on February 5, 1943, passed the following resolutions:

1. That there is at the present time no actual shortage of physicians in this county.
2. That we are opposed to the licensing of or granting temporary permits to physicians who have not provided themselves with licenses through the regular channels provided by the laws of the State of Florida.
3. That we are squarely behind the State Board of Medical Examiners in their efforts to protect the interests of Florida licensed physicians, both at home and in the armed services.
4. That our Senators and Representatives be contacted and urged to oppose any attempt to break down or alter our system of medical licensure.
5. That a copy of these resolutions be sent to the President and all other officers of the Florida Medical Association, to each member of the Board of Governors, the Board of Past Presidents, the Committee on Legislation and Public Policy, the State Board of Medical Examiners, the Secretary of every component County Society, the Editor of the Journal, the Governor of the State of Florida, the Secretary of each State Society in the United States and to every State Journal.

W. C. McConnell, President
A. M. Feaster, Secretary.

News Notes

Dr. Thomas Stringfield, II, of Waynesville was married to Miss Harriet Cutler Coburn of Asheville on February 3.

Tuberculosis is increasingly becoming a disease of older, occupied men. So much emphasis has been placed on tuberculosis as a serious disease of girls and young women that its greater havoc among men has not received the attention that it deserves. As a result of the more rapid decline of tuberculosis in females in this country there are today 132 deaths among males to every 100 deaths in females, and only at ages ten to thirty is the mortality higher in females.—From the Modern Attack on Tuberculosis by Henry D. Chadwick, M. D. and Alton S. Pope, M. D.

AUXILIARY

A TRIBUTE FOR DOCTORS' DAY

We write voluminously about great agressors and their bloody trails but few know of those men who fought for years, many losing their lives in the battle to make life safe. We honor Columbus and others because they sailed unknown seas and discovered new lands. Who honor those men who for years, with the unknown before them, submitted to experiments on themselves and discovered the microbes which defend them, often losing their lives to prove their observations and beliefs?

Kings and warriors have changed our destinies, but the Medical Profession and its protection have shaped and changed our civilization. Remove it today, and the speed of modern transportation would increase the ravages and the desolation of pestilences which destroyed other generations.

When illness comes, does the watcher at the bedside want to hear of statesmen and soldiers? No! The words which flood her being with relief and hope and courage come from the observer at the window, "The Doctor has come!" In those four words, the accumulated medical knowledge and experience of all times come to our protection and relief.

History is unjust and inadequate when it omits these benefactors and pioneers. The every-day world knows nothing or little of the weary pace of uncounted doctors, uncomplaining, unknown, unsung, whose work is their glory. We, your wives and families, realize this and we believe that the knowledge of the valiant struggles and sacrifices which have been endured to protect communities and guard individuals should be promulgated.

Today, we honor the pursuers of truth, the practitioners of the Medical Arts wherever they have lived, and regardless of time. We salute YOU, our husbands, our physicians! If the only certain happiness is doing good, then your satisfactions are unique. You preside in the struggle of life over death and ask neither notice nor appreciation. Space or time do not limit the giving of yourselves, and your reward is the inward rejoicing that you have done your best. As Physician and as Citizen, again we salute you, and pray that we may walk through the years beside

you, our love and respect sustaining you until we may enter with you into the Living Peace.

MRS. JOHN BONAR WHITE.

DOCTORS' DAY — MARCH 30

In these troubled days it will be well for us—the members of the Auxiliary to the Medical Society of the State of North Carolina—to pause, for a few moments, in the busy routine of "war time America" to take notice of the wonderful work our husbands and fathers are doing for suffering humanity.

A few years ago a movement was inaugurated by the Southern Medical Auxiliary to set aside March 30 every year as "Doctors' Day", and it is the opinion of many of us in this Auxiliary to the State Medical Society that there can never be a better time than this year to show our appreciation of the self-sacrificing efforts of the medical profession at home, in the camps, and on the fighting fronts.

Even if our days are over-crowded with work that is well worth while, we can in our separate auxiliaries plan some simple way to show the doctors of North Carolina, on that day, that their wives and daughters love them and honor them for their unselfish devotion to their God-given task of healing the bodies and ministering to the souls of men.

Doctors everywhere are not only combatting disease but are proving a bulwark of strength to those who need not only skill but sympathy and encouragement.

It will not be easy to plan a social gathering on Doctors' Day, but we can at least get our doctors together for a meal where they can find a few moments' respite from the strain and stress of a doctor's life. Good food, good music and interchange of ideas would vary the monotony of lives whose whole time is spent in service to their fellow man.

Last year two of our auxiliaries reported having observed Doctors' Day. May we lend our efforts to make this one hundred per cent this year?

We are making an earnest appeal to each auxiliary member in every district to do her part toward this end, and we feel that it will be done and done well.

MRS. J. B. CRANMER.

BOOK REVIEWS

Diseases of the Breast. Diagnosis, Pathology and Treatment. By Charles F. Geschickter, M.A., M.D., Director of The Francis P. Garvan Cancer Research Laboratory. With a special section on treatment in collaboration with Murray M. Copeland, A.B., M.D., F.A.C.S. 829 pages with 593 illustrations. Price, $10.00. Philadelphia: J. B. Lippincott Company, 1943.

The author and publishers are to be congratulated for this excellent monograph on the human breast. Our knowledge of the etiology, diagnosis and treatment of mammary diseases has been greatly advanced by recent work in endocrinology, surgery, radiology, pathology and gynecology. Dr. Geschickter himself has been a frequent contributor to the literature on this subject and in this monograph has collected our knowledge in a careful and painstaking manner. The subject as stated in the title is dealt with thoroughly, and this monograph should long remain a source-book for information on the subject. All types of lesions, whether anomaly, abnormality, infection, or tumor, are considered from the physiological and pathological as well as the practical clinical viewpoint. The book can be commended to all specialists as well as to the general practitioner.

The Anatomy of the Nervous System. By Stephen Walter Ranson, M.D., Ph.D., Formerly Professor of Neurology and Director of Neurological Institute, Northwestern University Medical School, Chicago. Seventh Edition, Revised. 520 pages with 408 illustrations, some of them in colors. Price, $6.50. Philadelphia and London: W. B. Saunders Company, 1943.

Ranson's **Anatomy of the Nervous System** has been the outstanding textbook on the subject for the last two decades. The present seventh edition, which was completed just before Dr. Ranson's death, maintains that scholarly thoroughness which has characterized earlier editions. A text of such excellence can emanate only from one who has not only taught the subject but has also contributed to research in the subject. Dr. Ranson, one of the leading neurologists in this country, has left in this book a worthy monument to his work and memory.

Essentials of Gynecology. By Williard R. Cooke, M.D., F.A.C.S., Professor and Head of the Department of Obstetrics and Gynecology, University of Texas. 474 pages with 197 illustrations, including 10 in color. Price, $6.50. Philadelphia: J. B. Lippincott Company, 1943.

This new text fills a long-felt need for a concise outline of the principles of gynecological practice. It covers all the essentials of the subject, with particular emphasis on diagnosis and treatment. There is an appendix describing the various procedures used in operative gynecology. The book is particularly appropriate to the needs of the general practitioner, since it treats of the patient as a whole rather than as a mere adjunct of some interesting pathological process. The publishers have applied the best in their art in making a readable and well

manufactured text. The illustrations are well chosen and helpful, except for some of the microscopic views which, like so many of these, mean little except to the expert microscopist who has no need of them. This new text can be recommended as a student text as well as for the general practitioner in need of revising his knowledge of the subject. The addition of a few references and some consideration of the hormonal aspects of gynecology would improve the value of the book.

A Textbook of Clinical Neurology. By Israel S. Wechsler, M.D., Clinical Professor of Neurology, Columbia University, New York; Neurologist, The Mount Sinai Hospital; Consulting Neurologist, The Montefiore and Rockland State Hospitals, New York. Fifth Edition, Revised. 840 pages with 162 illustrations. Price, $7.50. Philadelphia and London: W. B. Saunders Company, 1943.

In this new edition of a well-known text the author has included a consideration of recent advances in the study of headache, electroencephalography, degenerative diseases, the autonomic nervous system, and the use of chemotherapy in the treatment of meningitis. The book is written from a practical clinical standpoint, detailing methods of examination, diagnostic procedures and therapy. It is clearly written and can be recommended to students and practitioners of medicine who require a working knowledge of clinical neurology. Among the errors noted in the book are the statement that dystrophia adiposiogenitalis is caused by a chromophobe adenoma of the pituitary (p. 508) and that pheochromocytomas are the cause of Cushing's syndrome (p. 509). However, these are common errors in endocrinology and neither reflect upon the primary subject matter of the book nor detract greatly from its value as a textbook of neurology.

Diseases of the Gastro-Intestinal Tract (Oxford Medical Outline Series). By Asher Winkelstein, B.S., M.D., Associate in Medicine and Physician in Charge of the Gastro-Intestinal Clinic, The Mount Sinai Hospital, New York City; Associate in Medicine, (Gastro-Enterology), Post-Graduate School of Medicine, Columbia University, New York City. 195 pages. Price, $2.00. New York: The Oxford University Press, 1942.

The Oxford Medical Outline Series is an interesting experiment; and judging from this sample, it should be a successful one. All the common gastro-intestinal complaints are fully outlined by one whose wide experience fits him to select the essentials and leave out the non-essentials. It covers in full outline form the definition, pathology, etiology, incidence, symptoms, diagnosis, prognosis, and treatment of all the common diseases of the gastro-intestinal tract, and is a valuable means of obtaining a rapid review of the subject without wasting an unnecessary moment. It should be quite helpful to students preparing for examinations and to practitioners who must size up a patient's digestive symptoms without delay.

Contrary to Rumors—

the potency of Mead's Oleum Percomorphum 50% With Viosterol remains the same; namely, 60,000 vitamin A units and 8,500 vitamin D units per gram. Mead Johnson & Company, Evansville, Ind., U.S.A.

Postoperative Vitamin Deficiencies

Prolonged chronic illness followed by sharp limitation of diet during a period of preoperative preparation, especially when surgery of the gastrointestinal tract is contemplated, may result in a state of partial vitamin depletion. Most parenteral fluids routinely contain glucose, which sets up an additional drain on the vitamin B stores in the body. Postoperatively, nausea and vomiting occur frequently and there is often the necessity for complete restriction of food for days at a time.

This sequence of events was clearly reproduced in a case recently reported (Ann. Int. Med., 18:110, 1943). The patient developed a sore tongue and became uncooperative, disoriented, and confused. A dramatic change ensued after administration of riboflavin and nicotinic acid, with complete disappearance of the lesions within five days.

A number of laboratory procedures have been developed in recent years to augment the clinical diagnostic approach to vitamin deficiency disease, but many of them require special equipment and are not easily adaptable for routine clinical use. Physicians may obtain a list of vitamin values of foods and a bibliography of important and generally informative papers on vitamins by writing Eli Lilly and Company, Indianapolis.

New Squibb Capsules Supply Massive Doses of Vitamin D

To provide massive doses of vitamin D for use in the treatment of hypoparathyroid tetany and certain types of rickets, E. R. Squibb & Sons, New York, are now supplying capsules of Viosterol, each containing 50,000 U.S.P. units of vitamin D_2. The capsules are packaged in bottles of 40 and 100.

Clinically, vitamin D may be used to produce either of two effects, depending upon the dosage. In relatively low dosage, it exerts antirachitic activity, while in high dosage, ranging upward from 60,000 units daily, it raises a subnormal serum calcium level and is therefore useful in hypoparathyroid tetany. It is also sometimes administered as a single massive dose in the treatment of active rickets.

In hypoparathyroid tetany, an initial dose of eight or more Squibb Vitamin D Capsules daily is suggested, and a maintenance dose of two or four daily. In obstinate rickets, one capsule daily is recommended; in refractory rickets, one or more capsules daily; and in thoracic rickets, one capsule daily for two or three weeks.

In addition to the new Vitamin D Capsules, Squibb, of course, will continue to supply Viosterol in Oil, one gram of which contains the equivalent of 10,000 U.S.P. XII units of vitamin D.

Army-Navy "E" Presented to Ciba

How American medicine has met many challenging problems imposed by this global war was described by Albert Q. Maisel, war correspondent and author of "Miracles of Military Medicine," at a banquet for employees of Ciba Pharmaceutical Products, Inc., celebrating the presentation of the Army-Navy "E" to the company.

Earlier in the day Brig. Gen. S. V. Marietta, Commandant of Walter Reed Hospital, presented the "E" flag to Mr. J. J. Brodbeck, president of Ciba, and Sam and Carmelo Terranova, father and son who represented employees. Capt. Reynolds Hayden (MC), medical officer of the Third Naval District, presented "E" pins to Miss Helen Danow, Mrs. Grace Furneld, Mrs. Helen Hanlon, Miss Gertrude Hayes, Harry Bosshard and Rheinhold Uebele, acting for all employees.